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# Contents

## Original Articles



## Case Report



## Information

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# Chinese-German Journal of Clinical Oncology (《中德临床肿瘤学杂志》) 被EMBASE和Index Copernicus收录

《中德临床肿瘤学杂志》通过严格评审，于2010年被EMBASE和Index Copernicus收录。

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Index Copernicus (波兰《哥白尼索引》) 是由Medical Science International (国际医学) 创办的医药学、生物学国际检索系统，以收集生物学、医药学内容为主。近年来逐步扩大收录的学科范围，同时收集数学、物理、化学、地学等科学信息，成为世界性门户。每年,《哥白尼索引》根据期刊"科学质量"、"编辑质量"、"国际影响力"、"按时发行"和"印刷质量"等评价标准对其收录期刊进行多参数的质量评价。

《中德临床肿瘤学杂志》进入EMBASE和Index Copernicus数据库，是对期刊整体水平的肯定。我们将以此为契机，不断开拓进取，努力提高期刊影响力，更好地为肿瘤学研究人员服务！

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在此，我们衷心感谢广大编委、作者、读者对本刊的大力支持，并欢迎国内外从事肿瘤学及其相关领域研究的科研工作者踊跃向本刊投递高质量的稿件。我们愿意竭尽所能为您服务，共同搭建一个与全世界科研工作者相互交流的平台，使您的科研事业更上一级台阶！

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# Preliminary analysis of a clinical trial for three-dimensional conformal radiation therapy after conservative surgery*

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**Abstract** ***Objective:*** The aim of this study was to evaluate the efficacy, complications and cosmetic results of three-dimensional conformal radiation therapy for early breast cancer after conservative surgery. ***Methods:*** Among 80 patients, 44 were treated by modified radical mastectomy followed by adjuvant radiotherapy (modified radical mastectomy, MMT), 36 were treated with breast conservative surgery with adjuvant irradiation [breast-conservation therapy (BCT)]. Tangential fields were used to deliver 6 MV X-ray beams to a total dose of 50 Gy. Another 16 Gy was added to the tumor bed with 6–9 MeV electron beams for BCT. ***Results:*** In MMT group, the local control, metastasis-free and death were 41, 41 and 1 respectively; in BCT group, the local control, metastasis-free and death were 35, 35 and 0. The difference of the above two indicators between the two groups showeed no statistical insignificance ($P > 0.05$). In MMT group, 32 patients suffer radiation dermatitis above 2-level, 12 patients suffer radiation pneumonia, and 10 patients suffer edema of illness-side upper extremity; in BCT group, the above indicators were only 6, 2 and 1 respectively. Three months, six months and one year after radiation therapy, 90%, 92% and 95% patients were assessed as excellence in fine cosmetic state in BCT group. ***Conclusion:*** The effects of three-dimensional conformal radiation therapy after conservative surgery are the same as that of modified radical mastectomy, while the former has better cosmetic results and lower radiation therapy induced complications.

**Key words** radiation therapy; three dimensional conformal; breast conservative surgery; cosmetic result

Recently breast cancer is the most frequently diagnosed cancer in adult women. Currently the incidence of breast cancer is rising year by year in our country, and patients suffered from breast cancer are becoming much younger. How to provide comprehensive, individual treatment for early breast cancer for early breast cancer has been a subject of considerable controversy among the scholars in the field. Breast-conservation therapy (BCT), the use of breast conservative surgery and adjuvant radiation therapy, has been established as an indispensable treatment for early-stage breast cancer with excellent local control, similarly to modified radical mastectomy followed by adjuvant radiotherapy, and improve their quality of life [1]. We reported the clinic research outcomes of early breast cancer in this study.

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## Materials and methods

### Patients

During the period from June 2005 to June 2008, a total of 80 patients enrolled into the study were divided into two groups: 44 cases accepted modified radical mastectomy followed by adjuvant radiotherapy (MMT) and 36 cases breast conservative surgery with adjuvant irradiation (BCT). Breast cancer patients were enrolled into the study with following criteria: (1) tumor diameter ≤ 5 cm, (2) axillary lymph node negative or 1–3 nodes positive, (3) no distant metastases, (4) diagnosed as breast carcinoma by pathology. The patients with history of chest wall radiotherapy, collagen diseases, connective tissue diseases were excluded. The patient and tumor characteristics were listed in Table 1.

### Treatment course

*Breast cancer surgery*

In surgery, modified radical mastectomy was performed as below. The entire breast tissue was removed along with axillary dissection up to levels I and II, the pectoralis

**Table 1** The clinical comparisons of two groups

| Group | MMT group | BCT group |
|---|---|---|
| Case | 44 | 36 |
| Sex | Female | Female |
| Age (years) | 28–65 | 25–62 |
| Median age (years) | 45 | 43 |
| Histologic type | | |
| Invasive ductal | 36 | 32 |
| Other | 8 | 4 |
| Clinical stage | | |
| I | 32 | 28 |
| II | 12 | 8 |
| ER/PR status | | |
| Positive | 30 | 27 |
| Negative | 14 | 9 |

major and minor muscles were spared. Breast conserving surgery, as known as lumpectomy or, was the removal of cancerous area and a small amount of surrounding tissue to conserve the breast. The curved incision was used in the excision of the tumors in the supramammary field, otherwise radial incision in the inframammary field. In order to remove the lymph nodes with the levels I and II, a second incision may be made except breast tumor was in the axillary tail. Surgical margins were expected to achieve negative as far as possible diagnosed by intraoperative frozen section pathology to avoid secondary surgery. Metal markers were placed around the tumor bed to facilitate postoperation radiotherapy.

## Radiotherapy treatment

Two different treatment techniques were compared in this study. The technology of conventional radiotherapy was adopted in MMT group. The 3D conformal radiation therapy was used in BCT group. Patients in BCT group were treated in a breast board in the supine position with both arms extended overhead and supported by a dedicated arm rest. 3D Treatment Planning System-Pinnacle was based on CT images acquired by a dedicated radiotherapy AcQSim CT scan (Philips Medical systems). CT scans the entire chest with normal free breathing. The Clinical Target Volume (CTV) consisted of the whole breast parenchyma except for the skin area. The Planning Target Volume (PTV) was obtained by adding a 0.5–1 cm margin to the CTV. Organs at risk such as ipsilateral lung, heart, and chord spinalis were also outlined in every slice. The targets of MMT group included the chest wall and/or the supraclavicular, infraclavicular nodal areas. The dose of MMT group was total irradiation of TD 50 Gy/25 Fx. The targets of BCT group included the remaining whole breast and/or the supraclavicular, infraclavicular nodal areas. In BCT group, the treatment schedule consists of 33 fractions of 2 Gy within 6.5 weeks: 50 Gy to the entire breast plus a boost of 10 Gy to the tumor bed. According to the location of the tumor bed defined by metallic clips purposefully positioned at the time of the surgery and/or scar tissue, the boost dose of 16 Gy was administered to the tumor bed in single fractions of 2 Gy within 1.5 weeks by a 6 to 9 MeV electron field. Treatment site selection: in patients without axillary dissection, the breast, ipsilateral axilla, supraclavicular lymph nodes and apex of the axilla should be irradiated; in patients with axillary dissection, for those with negative or 1–3 positive axillary nodes, breast can be irradiated without lymph node regions (ipsilateral internal mammary nodes, axilla and supraclavicular lymph nodes), for those with more than 4 positive axillary nodes or 1–3 positive axillary nodes metastasis are found among less than 10 sampling lymph nodes, the breast, ipsilateral axilla, supraclavicular lymph nodes and apex of the axilla should be irradiated. Irradiation of the supra- and infraclavicular lymph nodes region was performed with a single anterior supraclavicular field. The anterior field was designed to encompass up to the cricothyroid membrane, the inferior border of the field was extended to match with the tangential fields on the level of the first rib's inferior border; the medial border of the field was along the midline of the body to the lateral edge of vertebral column, which was along the medial border of sternomastoid muscle; the lateral border of the field was extends to the outer border of the head of the humerus. Half beam technique was used to achieve geometric alignment between tangential and supraclavicular field. At the same time, gantry should rotate to the health side with 10–15 degrees to protect spinal cord, trachea and esophagus to reduce side effects of radiotherapy. Adaptive block should be used to reduce the radiation volume of the normal tissue. The tangential fields' borders: the superior border was inferior border of the clavicular-head, which was also the first rib's inferior border (inferior border of the supraclavicular field); the inferior border of the tangential fields lies 2 cm below the breast fold; the medial border was lateral to midline; the lateral border was midaxillary line or anterior axillary line. We selected the beam energy for the tumor bed according to the breast thickness variation.

## Adjuvant chemotherapy and endocrine therapy

All of the patients were treated with adjuvant chemotherapy before radiotherapy, both with CAF (cyclophosphamide 600 mg/m$^2$, adriamycin 60 mg/m$^2$, 5-FU 500 mg/m$^2$ d1 q3 weeks × 6). Adjuvant hormonal therapy with tamoxifen, if ER/PR was positive, was given after radiotherapy.

## Observation items

Response to treatment assessed after the median 18 months follow-up was divided into two types, using 2-point scale: local control, the patients experienced the

**Table 2** The comparisons of prognosis between two groups

| Group | Locoregional control | | Distant metastasis-free | |
|---|---|---|---|---|
| | *n* | % | *n* | % |
| MMT | 41 | 93 | 41 | 93 |
| BCT | 35 | 97 | 35 | 97 |
| $\chi^2$ | 0.69 | | 0.69 | |
| *P* | 0.403 | | 0.403 | |

comprehensive therapy were not local recurrence in the follow-up period; the other was distant metastasis-free.

### Toxicity

Radiation toxicity in both BCT and MMT group was evaluated according to the Radiation Therapy Oncology Group for Research and Treatment of Cancer (RTOG) morbidity scale. The side effects reported were skin toxicity, lung injury, edema of illness-side upper extremity and else. Skin acute radiotherapy toxicity was scored these items, a 3-point scale: grade1, if there was faint or dull erythema, epilation, dry desquamation, decreased sweating; grade 2, if there was bright erythema or patchy moist desquamation, moderate oedema, pitting oedema; grade 3, when confluent, moist desquamation other than skin folds or pitting oedema was present. The degree of radiation pneumonitis was described as below: grade 1, a mild nonproductive cough or forceful dyspnea; grade 2, required narcotic cough medicine, persistent cough, minor activities induced dyspnea; grade 3, narcotic cough medicine invalid, serve cough, resting dyspnea. Lymphoedema was also considered a most significant complication of locoregional treatment of breast cancer. The upper limb edema was using 3 scales: grade 1, upper limb circumference increased by 2–4 cm; grade 2, upper limb circumferences increase 4–6 cm; grade 3, upper into circumference > 6 cm.

### Cosmetic assessment

In scoring these items after BCT, such as breast size, breast shape, and shape of areola, the treated breast was compared with the untreated breast, using a 4-point scale: excellent (4) when compared to the untreated breast, minimal or no difference in size or shape or consistency (texture) on palpation of the treated breast. There might be mild thickening or scar tissue within the breast or skin, but not enough to change the appearance; good (3) mild asymmetry between the breasts (slight difference in the size or shape of the treated breast as compared to the opposite breast), mild reddening or darkening of the breast. The thickening or scar tissue within the breast causes only a mild change in the shape; fair (2) moderate deformity with obvious difference in the size and shape of treated breast. This change involved 1/4 or less of the breast. There was moderate thickening or scar tissue of the skin and the breast, and obvious color changes; and poor (1) marked change in the appearance of the treated breast involving more than 1/4 of the breast tissue. The skin changes were very obvious. There was severe scarring and thickening of the breast. A review panel consisting of physicians and patients scored the cosmetic results.

### Statistical analysis

Enumeration data were analyzed with $\chi^2$ test, measurement data were analyzed with *t* test.

## Results

### Treatment effect

The two groups of patients were followed up. The median follow-up time was 18 months (range: 3–26 months). The 2-year curative effects in of the patients were presented in Table 2. In MMT group, there were 41 cases (93%) of locoregional control, 41 cases (93%) of distant metastases-free, 1 patient (2%) had died. In BCT group, there were 35 cases (97%) of locoregional control, 35 cases (97%) of distant metastasis-free, no deaths. The rate of distant metastasis-free and locoregional control were not significantly different between the two treatment groups ($P > 0.05$), mortality was similar.

### Complications

The two groups were different degrees of response to radiotherapy, but tolerated, no one case was lost. Radiation injury standard was scored using the RTOG. In Table 3, the cases of acute toxicity were shown. 26 patients experienced grade 2 or 3 radiodermatitis in the MMT group, 10 cases in BCT group. 12 patients experienced grade 2 or 3 radiation pneumonitis in the MMT group, 2 cases in BCT group. 10 patients experienced edema in the MMT group, 1 patient in BCT group.

### Cosmetic results

Cosmetic outcomes in BCT group were assessed by doctors and patients. The excellent/good scores (Table 4) evaluated by doctor were 90%, 92%, 95% after 3-, 6-, 12-month follow-up, compared with 89%, 92%, 97% estimated by patients, respectively.

## Discussion

Recently, with changing lifestyle, the incidence of breast cancer is rising. Breast cancer is the most common malignant tumor, currently has become one of the most important diseases that threat to women's health. The end of the last century, randomized prospective study data from some foreign research institutions, such as the Milan National Cancer Institute, the European Cancer Research and Treatment Collaborative Group, the U.S.

**Table 3** Adverse reactions of two groups

| Adverse reaction | MMT | | | BCT | | | $\chi^2$ | $P$ |
|---|---|---|---|---|---|---|---|---|
| | I | II | III | I | II | III | | |
| Skin reaction | 12 | 25 | 1 | 28 | 10 | 0 | 7.84 | 0.005 |
| Lung reaction | 8 | 4 | 0 | 2 | 0 | 0 | 6.46 | 0.011 |
| Edema | 8 | 2 | 0 | 1 | 0 | 0 | 6.64 | 0.010 |

**Table 4** Cosmetic score in BCT group

| Cosmetic score | Physicians | | | Patients | | |
|---|---|---|---|---|---|---|
| | Three months | Six months | One year | Three months | Six months | One year |
| Excellent (4) | 18 | 19 | 22 | 17 | 18 | 22 |
| Good (3) | 14 | 14 | 12 | 15 | 15 | 13 |
| Fair (2) | 4 | 3 | 2 | 4 | 3 | 1 |
| Poor (1) | 0 | 0 | 0 | 0 | 0 | 0 |

NSABP and Denmark DBCG82TN [2], the data had proved the rates of tumor-free survival, recurrence-free survival and overall survival were not statistically different compared breast conserving therapy for early breast cancer with modified radical mastectomy followed by adjuvant radiotherapy. Liljegren *et al* [3] reported 5-year and 10-year postoperative local recurrence were 18.4%, 67.0%, postoperative adjuvant radiation is essential. In our study, the median follow-up time was short, 18 months, In BCT group, there were 35 cases of locoregional control, 35 cases of distant metastasis-free, no deaths. In MMT group, there were 41 cases of locoregional control, 41 cases of distant metastases-free, 1 patient had died. The rate of distant metastasis-free and locoregional control were not significantly different between the two treatment groups, mortality was similar. A number of studies [4] had reported that most (44%–85%) intra breast tumor recurrences after breast conserving therapy occur in close proximity to the tumor bed and surrounding tissue, thus providing the significance for an adjuvant radiotherapy limited to the area of primary tumor bed. Through the CT simulation analysis, the location of primary tumor bed was identified by the excision cavity or scar tissue after surgery or metallic clips purposefully positioned at the time of the surgery. Relatively, the excision cavity formed upon exudate might extend its size, skin scars might be mobile, but the metallic clips are seldom changed over time. So in many researches [5], the GTV was outlined by the position of metallic clips. The CTV was contoured by adding 15 mm of PTV. The PTV was obtained by 10 mm uniform expansion around the CTV. Due to the type of breast conserving surgery, the removal of cancerous area and surrounding tissue with a margin of 10 mm, the CTV was contoured by the rang of the metallic clips. The boost dose was administered by a 6 to 9 MeV electron field to the tumor bed, according to 3D conformal radiation treatment plans.

The two groups were different degrees of response to radiotherapy, but tolerated, no case was lost. According to RTOG, 26 patients experienced grade 2 or 3 radiodermatitis in the MMT group, 10 cases in BCT group. Although the skin had no filler or tissue compensator, the skin toxicity was significantly reduced in BCT group ($P < 0.01$), due to the skin area excluded from the CTV. 12 patients experienced grade 2 or 3 radiation-induced lung injury in the MMT group, 2 cases in BCT group. 10 patients experienced lymphoedema in the MMT group, 1 patient in BCT group. In our study, we exploited 3D conformal radiation therapy and wedge technology to obviously improve homogeneous dose distribution in the irradiated volumes and decrease the dose and volume in the irradiated normal tissues [7] such as the ipsilateral lung, the heart, compared with conventional radiotherapy techniques. The rate of radiation pneumonitis and edema decreased significantly ($P < 0.01$).

The cosmetic results after breast conserving therapy were assessed by both physicians and patients. The excellent/good scores evaluated by physician were 90%, 92%, 95% after 3-, 6-, 12-month follow-up, compared with 89%, 92%, 97% estimated by patients, respectively. However, there is no agreement on the number of years after which the cosmetic result stabilizes. Many studies [8, 9] found a stabilization of the proportion of patients with an excellent/good result over time. Zhang *et al* [10] reported that in the prospective multi-center research about cosmetic outcome after breast conserving therapy the excellent/good scores were 89.7%, 91.1%, 86.6% after 6-month, 1-year, 2-year follow-up, the recurrence and survival rate had no effect on the cosmetic results, the quality of life was improved. Conventional radiation dose distribution homogeneity is seldom achieved, related to the complex three-dimensional shape of the breast after breast-conserving surgery. I apply three-dimensional conformal radiation therapy treatment for breast cancer, with a better dose distribution and cosmetic results. Moreover the CTV excluded the skin, to minimize the skin dose and reduce the skin side effects and avoid affecting the cosmetic results. Yeo *et al* [11] analyzed 33 cases of breast cancer of

Chinese women and spouses from a psychological point of view, 80% of them were satisfied with the cosmetic results after BCT assessed by McNemar's test methods.

In summary, the power of this 3D conformal radiation therapy after breast conserving surgery for early breast cancer is to have the approximate short-time efficacy while having excellent/good cosmetic and functional result and decreasing the radiation-induced injury, compared with modified radical mastectomy followed by adjuvant radiotherapy. It is worthy of further promotion, but the long-term local control and survival rate remains to be seen.

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# The application of DCE-MRI in diagnosing breast cancer*

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**Abstract** ***Objective:*** The aim of the study was to further explore the diagnostic value of breast dynamic contrast enhancement (DCE), and improve specificity of breast cancer diagnosis. ***Methods:*** The 93 patients with 105 breast masses were performed with routine magnetic resonance (MR) scan and DCE scan. ***Results:*** 1. Morphological manifestations and pathologic findings: 105 masses of enhance forms could be divided into six types: (1) No enhancement, 9 masses (breast cyst); (2) The heterogeneous enhancement, 31 masses (fiber adenoma, 9; breast cancer, 11; mammary gland hyperplasia, 10; leafy tumor, 1); (3) The unheterogeneous enhancement, 42 masses (fiber adenoma, 5; the hyperplasia, 3; breast cancer, 33; leafy tumor, 1); (4) Ring enhancement, 17 masses (breast cancer, 15; fiber adenoma, 1 and inflammation, 1); (5) Reticular enhancement, 2 cases (gigantic breast, 1 and inflammation, 1). (6) Duct shape enhancement, 4 (hyperplasia, 1; duct carcinoma, 3). 2. Enhancement slope and pathology results: The maximum slope in 62 malignant masses was equally 19.19 ± 8.13, maximum slopes in 43 benign masses was equally 9.46 ± 6.64, the difference had a very significance ($P < 0.01$). In 42 masses with II type curves, the maximum slope of 24 malignant focuses were 17.52 ± 6.39, while 18 benign focuses 8.33 ± 5.47, the difference had a very significance ($P < 0.01$). Use a test-receiver to work curve (ROC curve) progress analysis, with 14.85 for critical point, sensibility for 67%, specificity for 83%; with 17.10 for critical value, the specificity was 100%. 3. Curve type and pathological results: According to general type standard, type I of single-phase curve, 20 masses; type II of platform type curve, 42 and III type curve type of washout, 43. A group of six kinds of forms were as follows: (1) No increased signal strength curve, 9 (cyst); (2) The curve signal strength slowly increasing, 6 (hyperplasia 2, fiber adenoma 2, chronic inflammation 1, duct carcinoma 1); (3) The intensity of curve after rapid increase early, continued to increase slowly 5 (hyperplasia 4, inflammatory breast cancer 1); (4) Curve early signal strength increasing rapidly formed the stop after middle-late platform (platform type), 42 (hyperplasia 9, fiber adenoma 8, leafy tumor 1, and breast cancer 24); (5) Early signal strength rapid increase arrived the peak then rapid declined (outflow type), 40 (hyperplasia 1, fiber adenoma 5, leafy tumor 1, breast 33); (6) Early signal strength increase quickly reached a peak, after platform period, then rising quickly again, and all of 3 for breast cancer. ***Conclusion:*** Enhancement morphological characteristics of breast cancer such as duct or ring enhancement had diagnostic value. Maximum slope in benign or malignant lesions, particularly in the differential diagnosis of type II curve played an important role. Formation mechanism of type II curve might be that an obstacle blood backflow of blood vessels by vascular tumor emboli or tumor compression.

**Key words** breast, neoplasm; magnetic resonance imaging (MRI); dynamic contrast enhancement (DCE)

Breast dynamic enhance MRI (dynamic contrast enhanced magnetic resonance imaging, DCE-MRI) in 1986 was first used in clinical, after which has been growing rapidly. It plays an important role in the differential diagnosis of malignant tumor, and has become a routine screening method for breast mass lesion. The application is based largely on breast cancer tumor blood vessels generation, the increase of tumor microvascular density, the increase of blood capillary permeability of breast cancer cells to the organization and markedly is different from benign lesions [1]. Dynamic enhance scanning parameters are more, mainly including four aspects: the enhanced morphology, signal strength, enhance slope and curve type, which can reflect the breast tumors from different aspects and the characteristics of the blood. Many scholars has used some parameters to identify breast benign

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and malignant lesions, and improved the level of the diagnosis of breast cancer [2]. However, some of the parameters and index have not yet reached an agreement [3, 4], and this paper discussed the related parameters, aimed to improve breast cancer diagnosis accuracy.

## Patients and methods

### Patients

From October 24, 2006 to March 5, 2011, 213 patients with breast mass were performed with MR. Of which, by the surgery/biopsy 62 lesions in 58 cases were confirmed for breast cancer and 43 benign lesions in 37 cases. Eliminating a patient with rheumatic heart disease, a total of 94 qualified patients were recruited. All for women, aged 26–70 years old, an averaged of 46.9 years old. Major clinical symptoms had breast lumps 48 cases, breast pain 32 cases, and spilled milk 13 cases. Seventeen cases were found by screening.

### MRI protocol

The routine and DCE-MRI were performed in all patients with PHILIPS Achieva 1.5 T superconducting magnetic resonance, orthogonal breast array coil, and the patients prone, breast natural trailer. Conventional T1WI and fat inhibition T2WI transverse and sagittal section were acquired using a spin-echo pulse sequence. DCE T1WI the fat inhibit scanning sequence, TR/TE = 3.7 ms / 1.9 ms, and flip angle 10°, and the matrix 256 × 256, a thick layer of 3–4 mm, at 1 mm, set 11 phases, each to time for 25 to 50 s, interval 10 s, and total dynamic enhance time about 8 min. The first phase was pre-contrast, and the second to eleventh phase were post-contrast. Gadolinium acid Portuguese amine (Gd-DTPA) was injected in the middle of the elbow fast push vein note, with 2 mL/s, and the dose of 0.1 mmol/kg. The acquisition data were transmitted to image workstation and processed with function software. The biggest increase in the slope of the tiles on the false choice lesions showed, the color of the biggest red level for areas of interest return-on-investment (ROI, size for 5–10 cm), and then by the workstation software rendering time-signal strength curve (T-SI curve, Fig. 1–8).

According to this study, dynamic curve had 6 kinds of forms: (1) the signal strength without increase; (2) the signal strength slowly increasing; (3) the early signal strength increasing rapidly then increased slowly; (4) the early signal strength increased quickly after formed the stop to middle-late platform (platform type); (5) early signal strength increasing rapidly reached peak, signal strength gradually after decrease (washout type); (6) early signal strength increased quickly to reach peak, then a platform period and rapidly rising again. According to the current literature general curve parting standards, they could be divided into three types: (1) to (3) formed curve for type I (one-way type) for benign lesions; (4) formed type II as a platform type, for benign or malignant lesions; (5) and (6) formed curve for type III as clear type, highly suggestive of malignant lesions. The biggest increase rate was calculated as flowing: $\Delta SI = [(SIC - SI) / \Delta t$, SI and SIC were respectively the signal strengths of the initial and the highest point during the most large slope, and $\Delta t$ was for duration time (Fig. 1–8).

## Results

### Morphology and pathology results

Enhancement forms of 105 lumps could be divided into six types: (1) No enhancement (9 lumps), all for breast cyst; (2) The uniform enhancement (31 lumps) including fiber adenoma (3), breast cancer (11), mammary gland hyperplasia (10), and leaf tumor (1); (3) Uneven enhancement (42 lumps) including fiber adenoma (5), the hyperplasia (3), breast cancer (33) and phyllodes tumor (1); (4) Ring enhancement (17 lumps) including breast cancer (5), fiber adenoma (1) and inflammation (1); (5) Grid enhancement (2 lumps) including mastitis (1) and gigatomastia (1); (6) Ductal enhancement (4 lumps) including hyperplasia (1) and ductal carcinoma (3).

### Enhance slope and pathology results

For 62 malignant lesions, the average maximum slope was 19.19 ± 8.13; for 43 benign lesions the average maximum slope was 9.46 ± 6.64, and the difference was significant ($P = 0.000$, $< 0.01$). In 42 type II curve lesions, the average maximum slope of 24 malignant lesions was 17.52 ± 6.39, the average maximum slope of 18 benign lesions was 8.33 ± 5.47, and the difference was significant ($P = 0.000$, $< 0.01$). With participants working curve (ROC curve) to analyze, to 14.85 as critical value, the sensitivity was 67%, and specificity was 83%; with 17.10 for critical value, the specificity was 100%.

### Curve type and pathology results

According to general type standard, 20 lesions belonged to type I single-phase curve, 42 to type II platform type curve and 43 to type III washout curve. This group manifested as six kinds of forms: (1) Curve signal strength without increasing including cyst (9 lumps); (2) Curve signal strength increasing slow such as proliferation (2), fiber adenoma (2), chronic inflammation (1), and ductal carcinoma (1). (3) Early strength curve rapid increase continued to increased slowly as proliferation (5) and inflammatory breast cancer (1); (4) Curve early signal strength increased quickly after formed the stop to middle-late platform (platform type), as proliferation (9), fiber adenoma (8), leaf tumor (1), and breast cancer (24); (5) Early signal strength curve rapid increased to peak,

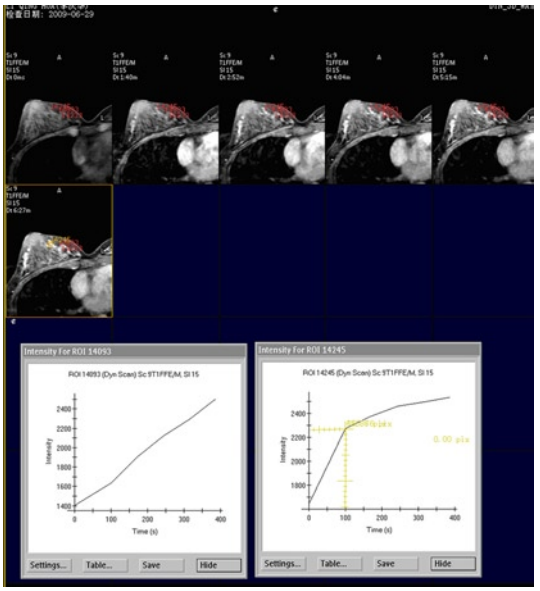

**Fig. 1** A 50 years old female. The right breast lesions outside quadrant with single-phase type on the dynamic enhance curve, pathology was mammary gland hyperplasia; The left ring lesions dynamic enhance curve of single slow rise type, pathological for inflammation

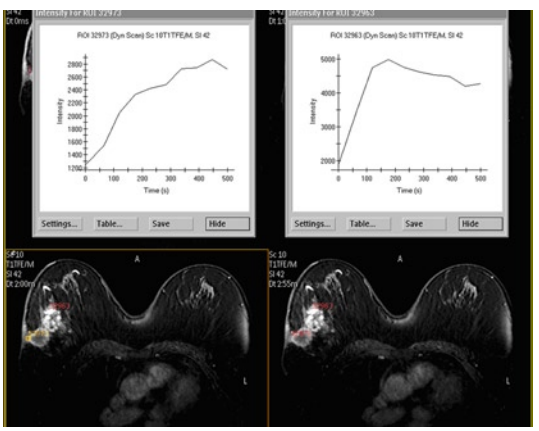

**Fig. 2** A 46 years old female. In different focus points, dynamic analysis strengthen curves were I and II types, respectively, but the biggest slope for 29.6, indicating that the vascular permeability increased, but blood backflow obstructed

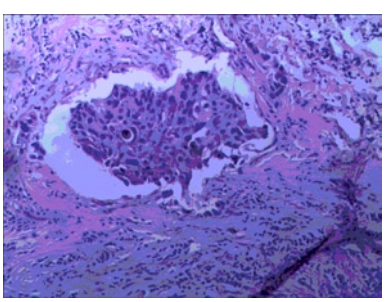

**Fig. 3** Pathology of Fig. 2 patient (HE staining x 100): infiltrating ductal carcinoma, level II, showing intravascular tumor emboli

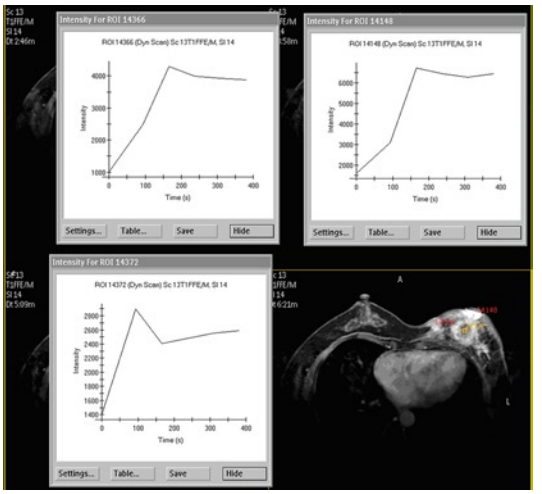

**Fig. 4** A 41 years old female. Such lesions were circular strengthening, and dynamic scanning showed washout type. Pathology: left infiltrating ductal carcinoma of breast

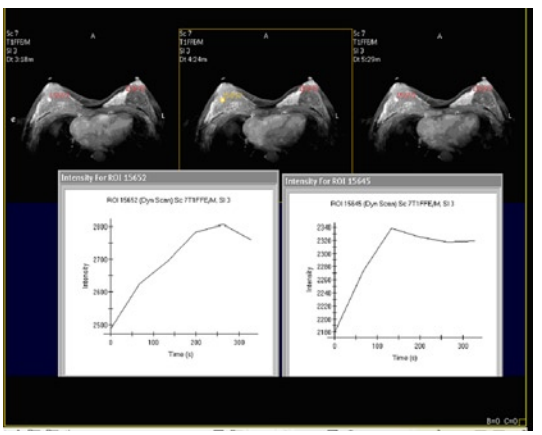

**Fig. 5** A 52 years old female. The right breast lesion showed slow rised dynamic curve type, left showed washout type. Pathology: the right breast hyperplasia, and left breast intraductal carcinoma

then gradually decreased (washout type) as proliferation (1), fiber adenoma (5), the leaf tumor (1), and breast cancer (33); (6) Curve early signal strength increased quickly to peak, after the platform period and then rising again, all for breast cancer (3).

Pathological types of 58 cases included infiltrating ductal carcinoma (46 cases), infiltrating lobular carcinoma (6), ductal carcinoma (3), mucous cancer (2), and inflammatory breast cancer (1 case).

## Discussion

### The enhance morphological features

The enhanced image morphology presented contrast agents space distribution in the mass, and was related to the distribution and density of vascular. The 105 lumps

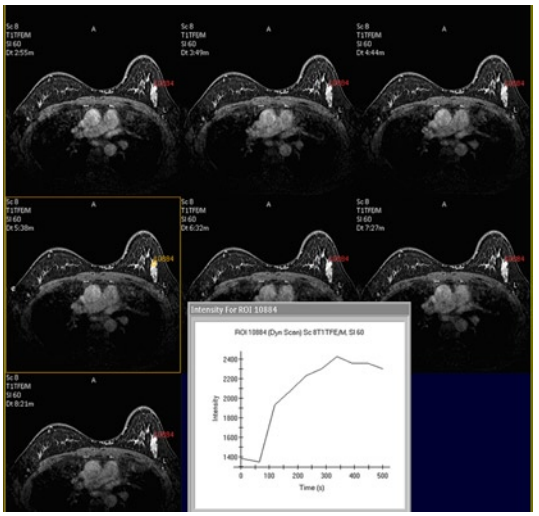

**Fig. 6** A 36 years old female. Ductal enhancement, dynamic curve was platform type, and maximum slope was 12.7 < 14.85. Pathology: dysplasia

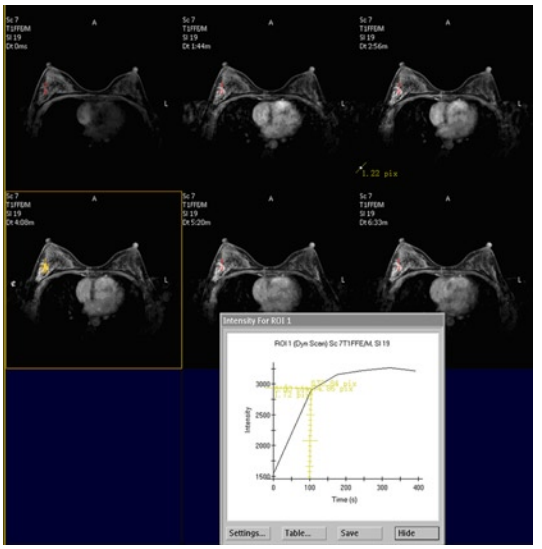

**Fig. 7** A 43 years old female. Dynamic curve was platform type, but the biggest slope was 14.9 > 14.85, and diagnosed for breast cancer

of enhancement forms could be divided into six types: (1) no enhancement; (2) homogeneous enhancement; (3) heterogenous enhancement; (4) ring enhancement; (5) gigatomastia enhancement and (6) ductal enhancement. Among them, no enhancement showed no blood supply and suggested benign lesions, such as the peripubertal or inflammatory lesions usually presented as reticulation enhancement. Homogeneous enhancement were visible in either benign or malignant lesions, and were identified by dynamic enhance parameters. Heterogenous enhancement often suggests malignant lesions. In this study 76.2% of heterogenous enhancement were breast cancer pathologically. Zhang *et al* thought that heterogenous enhancement of the internal structure was an important signs of invasive carcinoma. In their study all invasive carcinoma presented as heterogenous enhancement. However, some fiber adenomas also can show mild heterogenous enhancement, so diagnosis should be combined with other morphology and dynamic enhance scanning. Edge reinforced to be seen more breast cancers. In this group, of 17 edge focal enhancement 15 cases pathology were breast cancer, with 88.2% of specificity. So the sign for breast cancer was specific, consistent to other literature reported.

As for the ring of enhancement mechanism in invasive breast cancer, capillaries mainly germinating in the tumor edge area dense was the reason [5]. Immunohistochemical results showed that microvascular density values of edge part was greater than that of central part and the difference was significant. False positive ring enhancement can appear in the inflammatory cysts or fresh fat necrosis, but by internal signal characteristics it is not difficult to identify.

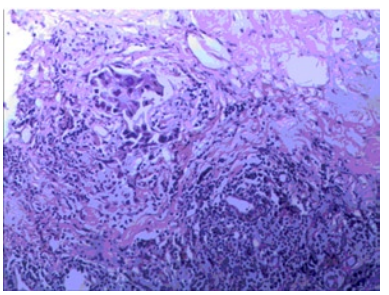

**Fig. 8** Pathology of Fig. 7 patient (HE staining × 100 ): infiltrating ductal carcinoma, showing tumor emboli within vascular

## Peak height

Peak height (PH) refers to the maximum dynamic curve signal strength. PH appears in the balance of DCE-MR period, which reflects the biggest ability gathering contrast agents of tumor organization, and is related to multiple factors such as the interstitial space external blood vessels, the size of the lesions, cell components, imaging sequences factors, so it couldn't predict the benign and malignant lesions. Our results supported this viewpoint.

## Enhance degree and the curve slope

A large number of domestic and foreign studies showed that mammary gland Gd-DTPA dynamic enhance slope curve could represent partly breast tumor angiogenesis. It was very important in identification of benign and malignant lesions and assessment of prognosis. Although difference of the scanning technology, the results were not same, but they strongly suggested that breast cancer had early enhancement. However a few benign lesions

also appeared early obvious enhancement [6]. To further improve breast cancer diagnosis specificity, some scholars studied maximum slope (Smax) [7]. The results showed that Smax of malignant lesions was significantly greater than that of benign lesions. In our cases, the dynamic parameters SmaxI between benign and malignant lesions was significantly different statistically. But Smax was related to many factors, some scholars suggest dynamic enhance parameters have no help in the diagnosis of breast cancer. Through further research we found that the same patients, if measuring different places, would come to different Smax. If not to collect the corrected Smax to judge, will reduce the sensitivity and specificity of the diagnosis. With ROC curve to analyze, to Smax 14.85 for critical point, the diagnosis sensitivity was 67% and specificity was 83%, to 17.10 as critical value, and the specificity was 100%.

### Enhance curve type

In present the type standard of DCE curve [8–11] was still controversial. To avoid the results different, combining domestic and foreign literatures, we suggest the common standards as follows: I type namely single-phase type (in dynamic observation time in horizontal or linear rise); II type that platform type (early signal strength increases, then keep state at the level); III type that is clear type or flushing type (early signal strength increased to peak, then decreased rapidly at least 10% of Smax). In fact, the 105 masses enhance scanning performance for six dynamic curve forms, among which the form (1) in cyst is venereal change, with the form (2) and (3) together could be classified into I type. This type of most benign lesions in the lesion without blood vessels or perfect development vessels; The form (4) is II type of platform of type, already visible in benign lesions or malignant lesions. It was reported in the literature that this type curve to identify the benign and malignant lesions [12] was little sense. However, by calculating the maximum slope and with the pathology results, we found that maximum slopes of benign and malignant lesions were different significantly, so using of such critical value can further improve the positive rate of breast cancer in type II curve.

The forms of (5) and (6) could be classified into type III, that is clear (flush or washout) curve. The characteristics of increasing and decrease rapidly accurately reflected that the malignant tumor endothelial cell growth is not complete and has high permeability, so type III has high specificity in the diagnosis of breast cancer. Mechanism of the form (6) curve might be the blood supply of lesion came from different blood supply artery, but remains to be accumulated material further study.

Through observing the pathological materials, we found that tumor emboli was found in lesions vascular in eight patients of 24 malignant diseases with type II curve, so we speculated that part reason for formation platform curve might be vascular block by tumor emboli. Pathological mechanism of the curve platform type in other 16 case might be oppression relevant or tumor necrosis, need further researches to be confirmed.

Because of less sample sizes, this paper has failed to multivariate statistical analysis with the enhanced form, slope, and curve of mass, which is the disadvantage of this study. We will further accumulate related data for further analysis.

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# Value of high-frequency ultrasonography with virtual touch tissue quantification in diagnosis of breast pure mucinous carcinomas

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**Abstract** ***Objective:*** The aim of our study was to analyze the characters of breast pure mucinous carcinomas on high-frequency ultrasonography with virtual touch tissue quantification (VTQ). ***Methods:*** A total of 12 patients (with breast pure mucinous carcinomas) and a group of 30 patients (with adenofibroma of breast) underwent breast examination with high-frequency ultrasonography to analyze the characters of images, and with VTQ to analyze the elastic character. ***Results:*** In the conventional ultrasound imaging, statistical differences were found between two groups in the shape, the boundary and the internal echo of the lesions. In the VTQ, the mean of shearing wave speed (Vs) in pure mucinous carcinomas was less than in adenofibroma of breast. ***Conclusion:*** Conventional high-frequency ultrasonography combining with VTQ have significant value in diagnosis of breast pure mucinous carcinoma.

**Key words** breast; pure mucinous carcinoma; ultrasonography; virtual touch tissue quantification

Breast mucinous carcinoma is a malignant breast tumor in a rare pathological type, accounting for all breast cancer 1% to 6% [1], due to special pathological changes and similarity in conventional ultrasound images to benign fibroadenoma which would be misdiagnosed. Virtual touch tissue quantification (VTQ) imaging, a newly developed elastography, evaluates tissue quantitatively to providing complementary informations to conventional ultrasound. This study used the conventional high-frequency ultrasound combined with VTQ technology on the breast of pure mucinous adenocarcinoma comparison with fibroadenoma, and inspected, observated and compared the sonographic features and flexibility characteristics in order to improve understanding of pure mucinous adenocarcinoma of the breast.

## Materials and methods

### Patients

Ultrasound was performed in the patients who underwent evaluation of breast lesions at our department from November 2010 to April 2012 and confirmed by pathology, 12 cases of patients with breast pure mucinous adenocarcinoma and 30 cases of patients with breast fibroadenoma were analyzed retrospectively, patients were all women, pure mucinous adenocarcinoma group aged from 42 to 83 years old, mean 61.1 ± 12.8 years; fibroadenoma group aged from 33 to 56 years old and mean 38.2 ± 10.9 years old.

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### Instruments and methods

Siemens ACUSON S2000 ultrasound diagnostic apparatus applicated, with Acoustic Radiation Force Impulse (ARFI) technology, high-frequency linear array probe 9L4, frequency 4–9 MHz.

Conventional ultrasound scanning was performed on the patients in the supine position, fully exposed breast, the nipple as the center, radial vertical and horizontal cut scanning in all quadrants, and according to the specific circumstances of the lesion adjusted the depth, gain, focus location of the images. The ultrasound characteristics including lesion shape, edge, border, traveling direction, internal echo, posterior echo were obtained.

VTQ was performed in the VTQ mode of ARFI technology by the same machine and the same transducer which was applied with light pressure to make complete contact with the breast but to let the patient in breath-hold. The region-of-interest (ROI) (size 0.5 cm × 0.5 cm) was placed entirely in the lesion, and the maximum depth of 5.5 cm. The shear wave velocity (Vs) was measured in the lesion, simultaneously measures in peritumoral glandular tissue (from the lesion 1–2 cm) and the normal glandular tissue

**Table 1** Comparison of conventional ultrasound performances of breast pure mucinous adenocarcinoma and breast fibroadenoma

| Ultrasonography | Pure mucinous adenocarcinoma | Fibroadenoma | $\chi^2$ value | *P* value |
|---|---|---|---|---|
| Shape | | | | |
| Round or oval | 3 | 24 | 8.60 | < 0.005 |
| Irregular in shape | 9 | 6 | | |
| Edge | | | | |
| Clear | 8 | 27 | 3.36 | 0.072 |
| Blurred or burr-like | 4 | 3 | | |
| Boundary | | | | |
| Interface sharp | 5 | 29 | 16.82 | < 0.005 |
| Strong echo halo | 7 | 1 | | |
| Mass orientation | | | | |
| Parallel | 7 | 25 | 2.86 | 0.12 |
| Not parallel | 5 | 5 | | |
| Internal echo | | | | |
| Uniform | 3 | 21 | 7.08 | < 0.01 |
| Uneven | 9 | 9 | | |
| Posterior echo | | | | |
| Enhance | 7 | 22 | 0.90 | 0.34 |
| Does not enhance | 5 | 8 | | |

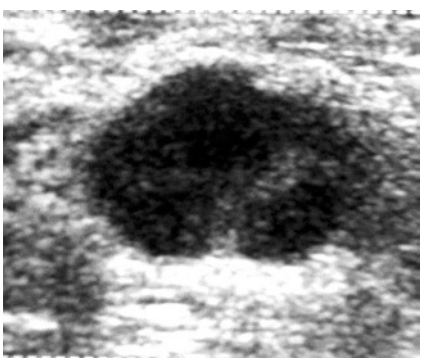

**Fig. 1** Conventional high-frequency ultrasound image of a pure mucinous carcinoma of breast. Irregular shape, clear margins, no capsule, showing the echogenic halo sign, hypoechoic internal echo unevenly, posterior echo enhancement

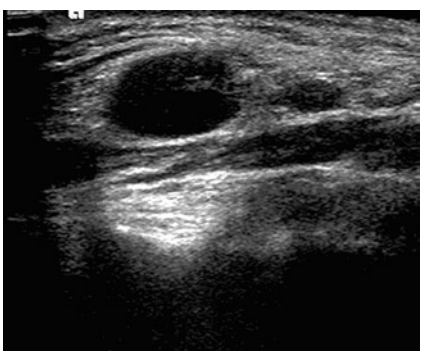

**Fig. 2** Conventional high-frequency ultrasound image of breast fibroadenoma. Regular shape, clear margins, complete envelope, low internal echo uniformly, posterior echo enhancement

of the same depth were performed, every location was measured 10 times, took the results to calculate the average. All images and data were stored in the CD analysis.

### Statistical analysis

Application of SPSS 13.0 statistical software for data analysis, in the conventional ultrasound imaging the differences of characteristics between pure breast mucinous adenocarcinoma group and fibroadenoma group were analyzed using the $\chi^2$ test; in the VTQ technology, the VTQ value (Vs) was showed by the mean ± standard deviation ($\bar{\chi} \pm s$), the difference of Vs between the two groups was analyzed by group *t* test, relationships between Vs of different location were examined using *q* test, $P < 0.05$ was considered statistically significant difference.

## Results

### Conventional high-frequency ultrasound performance

Comparison of conventional ultrasound performance in 12 cases of breast pure mucinous adenocarcinoma and 30 cases of fibroadenoma were shown in Table 1, differences in the shape, the boundary and internal echo were statistically significant ($P < 0.05$; Fig. 1, 2).

### VTQ

The comparison of VTQ values (Vs) in different location of two groups were shown in the Table 2. The difference of Vs in the lesion between the two groups was significant ($t = 8.42$, $P < 0.01$; Fig. 3, 4). In each group, the difference of Vs between inside the lesion and peritumoral glandular tissue was significant. While, the difference of Vs between peritumoral glandular tissue and normal

**Table 2** VTQ values of two groups and each group of lesions in different location

| Breast tumor | *n* | Different location Vs (m/s, $\bar{\chi} \pm s$) | | | *P* values | |
|---|---|---|---|---|---|---|
| | | Inside the lesion | Peritumoral | Normal | Internal/Peritumoral | Peritumoral/Normal |
| Pure mucinous adenocarcinoma | 12 | 1.15 ± 0.75 | 2.03 ± 0.43 | 2.32 ± 0.46 | < 0.001 | 0.078 |
| Fibroadenoma | 30 | 3.27 ± 0.56 | 2.37 ± 0.66 | 2.24 ± 0.37 | < 0.001 | 0.14 |

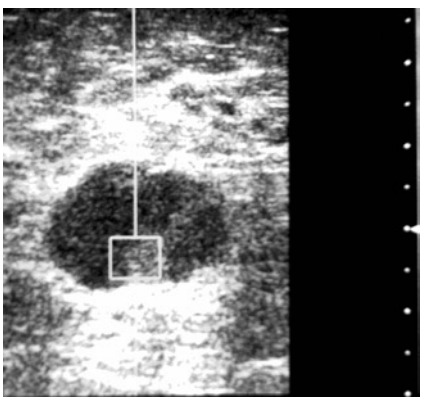

**Fig. 3** Ultrasound ARFI technique with VTQ value in a breast pure mucinous carcinoma (Vs = 0.78 m/s)

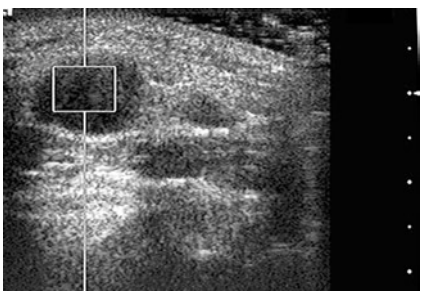

**Fig. 4** Ultrasound ARFI technique with VTQ value in a breast fibroadenoma (Vs = 2.91 m/s)

glandular tissue was not significant.

## Discussion

Breast mucinous carcinoma, also known as colloid breast cancer, ductal epithelium, is a rare type of invasive breast cancer occurred in postmenopausal women over the age of 50 mostly and the texture while clinical palping is soft or tough, active and adhesion flu. The characteristics of mucinous carcinoma is extracellular mucus in the tumor, and the mucous component in pure mucinous carcinoma accounts for 75% or more [2]. The tumor with smooth surface, clear boundary and expansive growth slowly has lower metastasis and significantly better prognosis than the other common types of breast cancers [3]. In the performance of conventional high-frequency ultrasound the breast pure mucinous adenocarcinoma is low echo, clear edge and more enhanced effect in posterior echo, similar to the characteristics of these in fibroadenoma. In this study, mostly irregular breast pure mucinous adenocarcinoma, was Oita leafy, clear most of the tumor edge, no envelope boundary expressed as echogenic halo sign, and fibroadenoma of breast are mostly round or oval shape, with intact membrane, smooth, sharp boundary. The internal echo of most of fibroadenoma is uniform low echo, while internal echo of pure mucinous adenocarcinoma is low or very low, mostly heterogeneous echo, with smaller scattered distribution of echo-free zone, which is considered owing to rich in mucus, and in a study of mucinous adenocarcinoma [4], the mass no apparent liquid zone, but showed cord-like hyperechoic and hypoechoic, disorganized non-homogeneous region, is one of the characteristics of ultrasound images of breast mucinous carcinoma. ARFI, a recently developed ultrasound elastography technique, uses probs to generate short-duration, high-intensity, acoustic pulse to generate localized, micron-scale displacements of tissue within the ROI, VTQ tracks a shear wave within the ROI that travels perpendicular to the transmitted longitudinal push pulse. Time to Peak analysis computes a numerical value of the shear wave speed obtained over the ROI which objectively reflects the hardness or elasticity of the target tissue, the greater the value, the stiffer a tissue. Krouskop *et al* [5] showed that various breast tissues have different elastic stiffness, invasive carcinoma having the lowest elasticity, followed by noninvasive carcinoma, fibrous tissue in the breast, normal glandular breast tissue, and breast fat tissue in that order. Meng [6] reported in 2011, VTQ values are significantly higher in malignant than benign breast lesions, and Vs are higher in both malignant and benign breast lesions than normal breast tissue, but most of the malignant tumors are invasive ductal carcinoma, not including a mucinous carcinoma. Elastography of breast tissue hardness is divided into five grades from low to high previously [7], the hardness of mucinous carcinoma is less than 3 grade. In this study, VTQ value of pure mucinous carcinoma of breast is lower than the surrounding normal breast tissue, is also significantly lower than the fibroadenoma. Fibroadenoma occurred in the end of the lobular duct and forms due to proliferation of interstitial cells and endothelial cells, stromal hyperplasia is more obvious. While the main component of pure mucinous adenocarcinoma is mucus. The based histopathological differences may be the reason of hardness of fibroadenoma higher

than pure mucinous adenocarcinoma. In this study, the difference of mean Vs of pure mucinous adenocarcinoma between normal glandular tissue and the peripheral tissue is not significant, which is different from the ordinary invasive ductal carcinoma from Meng, who pointed out that mean Vs of the peripheral tissues of invasive ductal carcinoma is significantly higher than the normal glandular tissue, reflecting the tissue of cancer infiltration to the surrounding glands. Pure mucinous adenocarcinoma is expansive growth and less infiltration, so it maybe relevant to its prognosis of lower transfer rate.

As ARFI imaging generates radiation pulse from the probe to promote the local tissue and results to a small deformation, compared to the other elasticity imaging techniques, ARFI takes advantages to not rely on the operator to push the organization, not be affected by adjacent hard tissue and be higher repetitive. VTQ technology can quantify the extent of flexibility of the tissue and thus more objectively reflect the flexibility or hardness. Because of the low incidence of breast pure mucinous adenocarcinoma and small sample size of this study, the Vs value would be biased, yet it needs to increase the sample size in order to further study of ARFI technology to the value of clinical diagnosis of breast mucinous carcinoma.

Simple summary, in conventional high-frequency ultrasound, breast pure mucinous carcinoma has the more irregular shape, boundary hyperechoic halo sign and heterogeneous inner echo texture which can be used as the identification with the fibroadenoma. On the basis of conventional ultrasound, combination with the VTQ technology, objectively reflects the elastic characteristics of tissue. Our result, the hardness of pure mucinous adenocarcinoma is lower than fibroadenoma, provides complementary information for the differential diagnosis of mucinous carcinoma, but also to make up for the awareness to breast elastic characteristics of the type of rare malignant tumor.

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# A Phase I trial of dose escalation of topotecan combined with whole brain radiotherapy for brain metastasis in lung cancer

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**Abstract** ***Objective:*** The aim of this study was to define the maximum-tolerated dose (MTD) and observe the toxicity of escalating topotecan combined whole brain radiotherapy for brain metastasis in lung cancer. ***Methods:*** Patients with brain metastasis of lung cancer received conventional fractionation radiotherapy, with 5 daily fractions of 2 Gy per week, the total radiation dose was 40 Gy, while the larger lesions were boosted to 50–60 Gy. The initial dose of topotecan was 1.0 mg/m$^2$. Escalation dose was 0.25 mg/m$^2$. Every cohort contained at least 3 patients.If no dose-limiting toxicity (DLT) was observed,the next dose level was opened for entry. These courses were repeated until DLT appeared. MTD was declared as one dose level below which DLT appeared. ***Results:*** Eighteen patients were recruited. Two cases of grade 3 leucopenia/neutropenia was observed as DLT at the level of topotecan 2.0 mg/m$^2$. MTD of topotecan was defined as 1.75 mg/m$^2$.The major side effects were leucopenia/neutropenia, nausea and vomiting. ***Conclusion:*** Topotecan combined with whole brain radiotherapy for brain metastasis in lung cancer is well tolerated. Maximum-tolerated dose of topotecan is 1.75 mg/m$^2$, once a week of a total of four.

**Key words** brain metastasis neoplasm/lung cancer; topotecan; radiotherapy; chemotherapy; maximum tolerated dose

Radiotherapy is always the main approach for brain metastasis, and the response rate of whole-brain irradiation is reported to be 70%–90%. However, the complete response remain lower and 50% of the patients have to be confronted with recurrence or failure in local control [1]. Topotecan, a antineoplastic drug specific in cell cycle, is an inhibitor of topoisomerase-I capable of passing through blood brain barrier and sensitizing radiotherapy [2]. Therefore, whole-brain radiotherapy combined with topotecan may have a superimposing and even synergistic effect, thereby achieving better results. Now, researches have been reported abroad on single topotecan combined with whole-brain radiotherapy [3, 4], implying a elevated local control rate. Now we reported our research.

## Materials and methods

### Inclusion criteria and clinical data

Patients with lung cancer brain metastasis proved by pathology or cytology test, aged between 18–70 years, with KSP > or = 70, normal in blood routine and hepatic/renal function, no chemotherapy within recent 3 months, no secondary malignancies or any other disease that needs hospitalization. All patients signed informed consent. Females in pregnancy or lactation were excluded.

Totally 18 cases enter into our trial, 10 males and 8 females, all aged between 36–70 years. The cases including 5 small cell lung cancer and 13 non-small cell lung cancer (6 squamous cell carcinomas, 6 adenocarcinomas, and 1 alveolar cell carcinomas). There were 8 patients with simultaneous lung cancer and brain metastasis without previous chemotherapy or radiotherapy, 10 with brain metastasis post first therapy for lung cancer, and 5 complicated with other visceral metastases.

### Regimens

Multi-Leaf Collimator whole-brain irradiation was performed with 6 MV X-rays, 2 fields/f/d, 5 d/w, and DT 40 Gy/20 f. For 6 large solitary lesions (> or = 2 cm in diameter at the end of whole-brain radiotherapy), three-

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**Table 1** Side effect in each group

| Adverse reaction | Grade | Topotecan dosage level (mg/m$^2$) | | | | | Incidence rate (%) |
|---|---|---|---|---|---|---|---|
| | | 1.0 | 1.25 | 1.5 | 1.75 | 2.0 | |
| White blood count | 1 | 1 | 1 | 1 | 1 | 3 | 38.8 |
| | 2 | 1 | 0 | 0 | 1 | 1 | 16.7 |
| | 3 | 0 | 0 | 0 | 0 | 2 | 11.1 |
| Absolute neutrophile count | 1 | 1 | 0 | 1 | 1 | 2 | 27.7 |
| | 2 | 0 | 0 | 0 | 1 | 1 | 11.1 |
| | 3 | 0 | 0 | 0 | 0 | 2 | 11.1 |
| Platelet count | 1 | 0 | 0 | 1 | 0 | 1 | 11.1 |
| Hemoglobin count | 1 | 0 | 0 | 0 | 0 | 1 | 5.5 |
| Nausea | 1 | 1 | 1 | 0 | 0 | 1 | 16.7 |
| Vomit | 2 | 0 | 0 | 1 | 1 | 1 | 16.7 |
| Decreased food appetite | 1 | 2 | 1 | 1 | 2 | 3 | 50.0 |
| Diarrhea | 1 | 0 | 1 | 0 | 0 | 0 | 5.5 |
| Radiodermatitis | 1 | 1 | 1 | 2 | 1 | 2 | 38.8 |
| Febrile | 1 | 0 | 0 | 0 | 0 | 1 | 5.5 |

dimensional conformed radiotherapy (3DCRT) was used, with local dosage increase to 50–60 Gy. Topotecan was started from d1 of radiotherapy at 1.0 mg/m$^2$ once a week for 4 weeks, administered intravenously within 1 h prior to irradiation. Based on the modified Fibonacci method [5], an increment of 25% of the initial dosage, i.e. 0.25 mg/m$^2$ was adopted between every two groups. At least three patients were sequentially into each dosage group. The next dosage group was opened if there was no dose limiting toxicity, but repeated test was not permitted on a same patient. If dose-limiting toxicity (DLT) was reported in 1 patient in a dosage group, test under the same dosage was repeated in another three subjects. Then the test moved on to the next dosage if there was no DLT, or stopped otherwise.

### Determination of maximum tolerated dose (MTD)

MTD, the level inferior to DLT for an increment, was defined as the dosage causing an interruption more than 1 week because of side effects of chemotherapy/radiotherapy, or potentially threatening lives of patients as estimated. The criteria included: (1) Non-hematological toxicity; > or = 50% patients with grade-2 impairment in hepatic or renal function or grade-3 toxicity; grade-4 nausea and vomiting. (2) Hematological toxicity: grade-4 leucopenia or neutropenia in patients supported with colony stimulating factor (CSF), or grade-3 leucopenia lasting for no less than 7 days or grade-3 leucopenia with fever, or thrombocytopenia or hemoglobin reduction in grade 3 or 4.

### Parameters under observation

A common toxicity criterion of NCI-CTC 3.0 was used to evaluate the toxicity. Therapeutic response was evaluated according to UICC to be complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD). All examinations were done for the baseline within 1 week prior to therapy, and repeated at week 4 after therapy, including routine physical examination, three routines, hepatic/renal function, chest X-ray, abdominal B-scan ultrasonography and MR imaging or contrast-enhanced CT for brain.

**Table 2** Response of different Topotecan dosage level

| Therapeutic effect (case) | Topotecan dosage level (mg/m$^2$) | | | | |
|---|---|---|---|---|---|
| | 1.0 | 1.25 | 1.5 | 1.75 | 2.0 |
| CR | 0 | 1 | 0 | 1 | 2 |
| PR | 2 | 1 | 3 | 2 | 4 |
| SD | 1 | 1 | 0 | 0 | 0 |

## Results

Tolerance: five dosage levels were used, including 1.0, 1.25, 1.5, 1.75 and 2.0 mg/m$^2$. A grade-3 bone marrow suppression was observed in one patient at the dosage of 2.0 mg/m$^2$ post 36 Gy whole-brain irradiation, i.e., the first DLT. The test was stopped and the same dosage was tested on another 3 patients, where another grade-3 bone marrow suppression occurred. Therefore 2.0 mg/m$^2$ was determined to be the DLT, and the level inferior to it for an increment was recognized as the MTD (1.75 mg/m$^2$).

Toxicity: the main toxicity was bone marrow suppression and gastrointestinal reaction (Table 1).

Recent efficacy: findings of enhanced MRI or CT at 1 month after therapy proved 4 CRs, 12 PRs, 2 SDs and 2 CRs out of 6 patients with solitary lesion treated with 3 DCRT with local dosage increment, at topotecan dosage of 1.25 mg/m$^2$ and 2.0 mg/m$^2$ respectively (Table 2).

## Discussion

Incidence of brain metastasis of lung cancer keeps ris-

ing along with rising yearly incidence of lung cancer. The most effective approach for brain metastasis is single whole-brain radiotherapy [6]. The progression of chemotherapy in this area has been hindered by the presence of blood brain barrier. However, researches on drugs capable of passing through the barrier, such as Vm-26 and topotecan, have increased gradually, and one of the focuses has been the comprehensive approach involving with whole-brain radiotherapy combined with chemotherapy for a better local control rate of brain metastasis [7].

Now, both overseas and domestic reports [8, 9] proves the superiority of combination between Vm-26 and whole-brain irradiation in lung cancer brain metastasis over single radiotherapy, while overseas researches in phase I and II have been available on whole brain radiotherapy combined with topotecan in brain metastasis [3, 4, 10]. Most of these researches adopted daily administration of topotecan combined with whole brain irradiation, and the daily MTD reported 0.4–1.0 mg/m$^2$/d proved tolerable and capable of improving the local control rate of brain metastasis. The main side effects included bone marrow suppression. No similar researches have been reported in China, except for some clinical trials [11] achieving good responses to topotecan combined with radiotherapy in lung cancer. In our trial, 2 patients during treatment of topotecan 2 mg/m$^2$ weekly combined with whole-brain radiotherapy manifested grade-3 bone marrow suppression, who accomplished their radiotherapy after symptomatic treatment and G-CSF treatment. The MTD was 1.75 mg/m$^2$/w. The dose limiting toxicity mainly included bone marrow suppression, followed by gastrointestinal reaction, all of which seemed tolerable given close observation and treatment in time.

In a word, it is feasible clinically to treat lung cancer brain metastasis comprehensively with whole brain radiotherapy combined with topotecan, and the MDT of topotecan is to be 1.75 mg/m$^2$/w, based on which a randomized clinical trial is ongoing.

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# Cryorecanalization after cryosurgery for immediate treatment on central airway obstruction via flexible bronchoscope

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**Abstract** ***Objective:*** In order to achieve immediate relief of central airway obstruction caused by malignant tumor after interventional therapy, we observed the efficacy and safety of cryorecanalization after cryosurgery via flexible bronchoscope. ***Methods:*** A total of 64 cases of patients in all suffered from central airway obstruction were observed and treated by applying cryorecanalization after cryosurgery via flexible bronchoscope. Divide the operation into two steps, including cryosurgery and cryorecanalization. Evaluate the therapeutic effect immediately after the treatment, wherein the evaluating indicator includes preoperative and postoperative dyspnea indexes, quality of life score, bronchoscopy, etc. The surgical safety assessment is mainly by observing the risk of bleeding in the surgery. ***Results:*** Forty cases (62.5%) has postoperative dyspnea score improved at least one level compared with preoperative dyspnea score, 24 patients (37.5%) have no significant improvement on dyspnea score. Quality of life score (Karnofsky score): preoperative 52 ± 18.7 points, postoperative 70 ± 9.2 points. Bronchoscopy review: complete success in 12 cases (18.8%), partial success in 45 cases (70.3%), no success in 7 cases (12%). 89.1% overall clinical efficiency was achieved. In the surgery, the control to bleeding was satisfactory since no severe bleeding, moderate bleeding in 14 cases (21.9%) and mild bleeding in 50 cases (78.1%) were found as well as rigid bronchoscope was free. ***Conclusion:*** The central airway obstruction can be immediately relieved by cryorecanalization after cryosurgery via flexible bronchoscope with satisfactory effects and higher surgical safety.

**Key words** cryosurgery; cryorecanalization; bronchoscope; central airway obstruction

In respect of patients with advanced lung cancer, when tumors cause central airway obstruction, coughing, hemoptysis, shortness of breath or choking and a series of symptoms are generated, secondary obstructive pneumonia due to airway obstruction is very difficult to treat, so the severe airway obstruction often leads to the threaten of lung cancer patient's life and life quality decline [1–3]. The key point of relieving the symptoms is clearing away tumors in airway as soon as possible, by which the patients can acquire conditions for further treatment. At present, a variety of tracheal interventional techniques have been applied for the treatment of central airway obstruction [4–8]. Bronchoscopic cryosurgery can be operated via the flexible bronchoscope so as to be widely applied at present. More treatment reports are submitted [9, 10], while the method has defects. Bronchoscopic cryosurgery are incapable of immediately clearing away the tumor tissue in the airway, so the secondary treatment is required and the airway can be reopened after the removal of necrotic tumor tissue. In order to achieve the airway patency by one-time treatment, the tail end of the rigid bronchoscope is used after cryosurgery for physically cutting off the tumor in the airway [11]. However, the rigid bronchoscope has higher requirements on anesthesia and respiratory support techniques applied to patients, and because the rigid bronchoscope cannot be bent, this mode is difficult to the upper lobe bronchus lesion and thus is still insufficient. We try to applying cryorecanalization after cryosurgery to achieving a one-time removal of tumors in the airway via flexible bronchoscope aimed at immediately relieving airway obstruction. This therapy mode has achieve a better therapeutic effect and now results are reported as follows.

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## Materials and methods

### Patients information

A total of 64 cases enrolled in this group from April 2010 to December 2011, including 48 males and 16 females, mean age of 64 ± 8.4 years. All cases respectively

have central airway obstruction in varying degrees before surgery, resulting from lung cancer as a primary disease in 53 cases (82.8%), of which squamous cell carcinoma in 38 cases (71.7%), adenocarcinoma in 15 cases (28.3%). In addition to lung cancer, laryngocarcinoma in 4 cases (6.3%) and esophageal cancer in 7 cases (10.9%), and all cases obtained pathological diagnosis, and were advanced or metastatic and inoperable patients. The distribution of the obstruction part of the airway was seen in Table 1. All of 64 cases had cough, hemoptysis, dyspnea, fever, obstructive pneumonia or obstructive atelectasis in varying degrees before surgery. All patients were required to carry out bronchoscopy and chest CT examination in order to define the lesions.

**Table 1** Obstruction part of the airway under bronchoscope

| Obstruction part of airway* | *n* | % |
|---|---|---|
| Trachea | 16 | 25.0 |
| Left principal bronchus | 14 | 21.9 |
| Right principal bronchus | 21 | 32.8 |
| Intermediate bronchus | 13 | 20.3 |

* The determination of the airway obstruction part is accordance with the upper border of tumor in the airway

## Surgical instruments

The cryosurgery apparatus adopted type K300 cryosurgery therapeutic apparatus and a flexible cryosurgery probe (Beijing Kooland Medical Equipment Co. Ltd., China), with the probe diameter of 1.9 m, the length of 90 cm and the tail-end length of 5 mm. Carbon dioxide was taken as a cryosurgery air source. The type of flexible bronchoscope was Olympus BF-1T60.

Argon plasma coagulator (APC) (ERBE, Germany Company) was adopted for hemostasis, wherein the diameter of APC catheter was 1.5 mm.

## Surgical method

*Pretreatment preparation*

Pre-treatment review of patients with chest X-ray and chest CT helped us to grasp the extent of airway lesions, routine ECG, lung function, blood gas analysis, blood coagulation time, etc. in order to assess whether to tolerate treatment and predict risk. Fasted in 4 h before surgery, 0.5 mg of atropine applied for intramuscular injection at 30 min before surgery. During surgery, patient was preferably supine, and electrode plate was connected to the upper arm or leg to prepare for the use of APC. 4% tetracaine spray was to make nasal and throat mucous membrane subjected to surface anesthesia, propofol, fentanyl, etc. were intravenously and the orotracheal intubation was carried out until the patients had no consciousness and the surgery was started after the intubation was succeeded.

*Operation method*

The surgery was divided into two steps. Firstly: cryosurgery. The flexible cryosurgery probe was sterilized with 75% alcohol and was inserted through a bronchial work canal; the cryosurgery generally proceeded at the tumor root; if the tumor was more diffuse, a freezing point was set every 3–5 mm, natural rewarming was realized after freezing for 2 min, repeated the cycle until the visible tumors were frozen. Secondly: cryorecanalization. The cryorecanalization method help remove tumor tissues that have been cryoablated; the end of the cryosurgery probe was vertically inserted into the tissues; the pedal was treated to freeze for 15–20 s, the cryosurgery probe and the bronchoscope were simultaneously extracted, the tumor tissues were attached to the end of the cryosurgery probe and were taken out of the body together; and after rewarming, the tissues automatically fall off from the cryosurgery probe. These two steps could be repeated until the tumor in the airway was removed and the airway was reopened (Fig. 1–4).

Argon plasma coagulation was used to stopping bleeding. The electrically coagulate was at the power of 20–60 W with the argon gas flow of 0.5–2 L/min. When APC electrode was inserted into work canal and exposed out of by 1 cm, the electric coagulation was started.

*Evaluation of therapeutic effect*

The effects evaluation indicator included preoperative and postoperative dyspnea index, quality of life score and bronchoscopy. The dyspnea index and the quality of life score were evaluated by adopting a self-administered rating scale method issued on the second day after surgery. The scoring criteria referenced to NYHA. The quality of life score adopted Karnofsky score. Bronchoscopy was proceeded after the surgery immediately. The therapeutic effected for reopening airway stenosis caused by malignant lesion were as follows: (1) Complete success: the lesion in cavity was completely removed and the functions were restored to be normal; (2) Partial success: the lumen had residual tumors, but allowed the BF-1T60 bronchoscope to smoothly pass through; (3) No success: no clinical subjective and objective improved evidence was found out. Complete and partial successes were count as clinical success [12].

*Evaluation of surgical safety*

The key point of evaluate the surgical safety was to observe the bleeding risk in the surgery. Divided the bleeding risk into 3 grades: mild bleeding, using local attraction, or spraying brine ice or epinephrine to stop bleeding; moderate bleeding, requiring to additionally used APC to stop bleeding; severe bleeding, stopping bleeding requiring to use other rescue measures, such as blood transfusion, duration extension of mechanical ventilation, emergency thoracotomy, etc. or surgery failed due to bleeding.

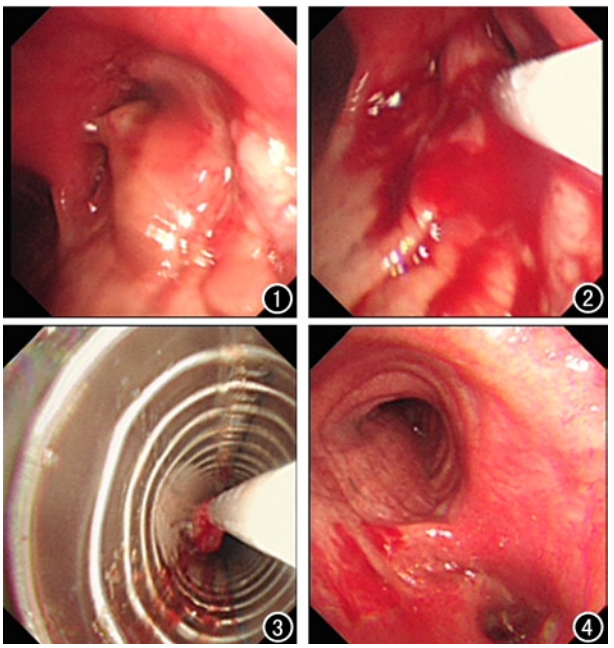


**Fig. 1** Right principal bronchus had been obstructed by tumor completely

**Fig. 2** The tumor was treated with cryotherapy, simultaneously visible tissue edema and errhysis

**Fig. 3** Tissue adhesion in freezing probe was taken out of the body

**Fig. 4** After the treatment airway substantially unobstructed, evaluation of efficacy for partial effective

## Results

This group of patients could well tolerate the surgery within 35–184 min (87 ± 26 min), without serious adverse events or intraoperative death in surgery. Some patients were subjected to intraoperative oxygen saturation decrease which could be alleviated after stopping operation and oxygenating 2–3 min. No perforation in the airway wall, respiratory and cardiac arrest and other serious complications were found out.

The evaluation of therapeutic effect were conducted on this group of patients after surgery, 40 cases (62.5%) had postoperative dyspnea score improved at least one level compared with preoperative dyspnea score, 24 patients (37.5%) had no significant improvement on dyspnea score. Quality of life score (Karnofsky score): preoperative 52 ± 18.7 points, postoperative 70 ± 9.2 points. Bronchoscopy review: complete success in 12 cases (18.8%), partial success in 45 cases (70.3%), no success in 7 cases (10.9%). 89.1% overall clinical efficiency was achieved.

It was satisfactory with the control to bleeding during surgery since no severe bleeding, moderate bleeding in 14 cases (21.9%) and mild bleeding in 50 cases (78.1%) were found. No rigid bronchoscope for stopping bleeding or removing necrotic tissue was used for all surgery.

## Discussion

In respect of airway obstruction caused by tumors in central airway, it is a key for successful treatment by applying the interventional therapy technology to quickly remove the tumor tissue and further make the airway reopened. The cryosurgery via bronchoscope adopt soft probes, can operate through work canal of the flexible bronchoscope and have the advantages of flexibility, simplicity and convenience, so the cryosurgery are widely applied to the treatment on tumors in the airway. At present, many successful stories have been reported with satisfactory outcome [13, 14]. However, there are also problems in clinical application. After the cryosurgery, the frozen tumor tissue is not immediately necrotized and drops off and the secondary surgical is required to remove necrotic tissue, resulting in that symptoms of patients subjected to cryosurgery cannot be relieved immediately; on the other hand, the carbon dioxide cryosurgery probe currently adopts a blunt probe, which cannot be inserted inside the tumor, resulting in superficial freezing range; and in respect of the larger tumor, cryosurgery is still difficult to make all the tumors necrotize. To resolve these problems, Hetzel [12] reported that 60 cases suffered from airway obstruction are treated by separately adopting a cryorecanalization method. This method is used for directly and repeatedly carrying out cryorecanalization on tumors in the airway, complete success and partial success achieve 83%, but 6 patients have a lot of bleeding with the amount of 100–300 mL. Schumann [15] *et al* use the same methods to treat 225 cases, total effective rate was 91.1%, but 13.8% of patients are required to combine rigid bronchoscope for stopping bleeding and so on. The tumors in the central airway are directly cleared away by using the cryorecanalization without pretreatment, larger cryorecanalization tissue has risk of increasing bleeding, although the cryorecanalization may instantly relieve airway obstruction.

The adopted cryosurgery before cryorecanalization can make up the defects of a single therapy to a certain degree and improve surgical safety and efficacy. The first step in the therapy mode is to freeze the tumors, on the one hand, the frozen tumor cells are inactivated, and on the other hand, the local blood vessels can be damaged, which leads to local micro-thrombus formation and creates the conditions for reducing bleeding when the necrotic tissue is removed; the second step is cryorecanalization, necrotic tissue can be removed with high efficiency; the cryosurgery at prophase has destroyed local blood vessels, so the risk of bleeding is also greatly reduced during cryorecanalization.

This group of patients is satisfied with short-term therapeutic effect after treatment, with complete success and partial success up to 89.1%. The life quality of patients is remarkably improved; the quality of life score

(Karnofsky score) is improved from preoperative 52 ± 18.7 points to postoperative 70 ± 9.2 points, on one hand, due to improved lung function, the patient's activity tolerance is improved; on the other hand, pulmonary infection is effectively controlled, benefiting from hemoptysis of the postoperative patients. In respect of the dyspnea remission, the dyspnea score of 40 postoperative patients (62.5%) is improved by more one grade, but part of patients has no improvement on conscious dyspnea. Due to non-serious airway obstruction and a small amount of daily activities of preoperative patients, dyspnea is not obvious and further the postoperative dyspnea is not obvious. But for central airway obstruction, even if the obstruction is not severe, when the patient has no obvious dyspnea, the interventional therapy should be actively carried out. When the central airway is severely obstructed, the surgical time is prolonged and hypoxia is easy to generate during surgery, resulting in an increase of surgical difficulty and danger.

Cryorecanalization after cryosurgery has higher surgical safety. This group of patients has no severe intraoperative bleeding, moderate bleeding in only 14 cases and mostly mild bleeding. The bleeding can be stopped by simple treatment. Meanwhile, this therapy can be accomplished entirely under the flexible bronchoscope simply and conveniently.

This study mainly observes the short-term efficacy and safety of the therapy method of cryorecanalization after cryosurgery. Due to the progress of tumor, the therapeutic effect of the surgery is difficult to maintain if no further postoperative therapy is carried out. Therefore, this therapy method is mainly used for relieving symptoms in short term and provides the necessary conditions for tracheal stent placement and follow-up treatment such as radiotherapy and chemotherapy and so on. Patients who receive poor effect mainly because of long distance of airway obstruction, deep position and relatively diffuse tumor found during surgery, surgical instruments have been unable to reach the deep part of bronchus. Therefore, it is important to accurate assess the obstructed part by dynamically observing preoperative CT changes.

The method of cryorecanalization after cryosurgery via flexible bronchoscope to treat central airway obstruction is a new treatment mode. Our initial experience finds that the combined therapy obtains satisfactory overall therapeutic effect and high surgical safety.

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# Predictive factors of lymph node metastasis in intramucosal poorly differentiated early gastric cancer and their impact on the laparoscopic surgery*

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**Abstract** ***Objective:*** The aim of this study was to identify clinicopathological factors predictive of lymph node metastasis (LNM) in intramucosal poorly differentiated early gastric cancer (EGC), and further to expand the possibility of using laparoscopic surgery for the treatment of intramucosal poorly differentiated EGC. ***Methods:*** Data from 65 patients with intramucosal poorly differentiated EGC and surgically treated were collected, and the association between the clinicopathological factors and the presence of LNM was retrospectively analyzed by univariate and multivariate logistic regression analyses. ***Results:*** Univariate analysis showed that number of tumors, tumor size and lymphatic vessel involvement (LVI) were the significant and independent risk factors for LNM (all $P < 0.05$). The LNM rates were 5.0%, 18.2% and 66.7%, respectively. There was no LNM in 31 patients without the three risk clinicopathological factors. ***Conclusion:*** The number of tumors, tumor size, and LVI are independently associated with the presence of LNM in intramucosal poorly differentiated EGC. Thus, these three risk factors may be used to set as a simple criterion to expand the possibility of using laparoscopic surgery for the treatment of intramucosal poorly differentiated EGC.

**Key words** poorly differentiated early gastric cancer; early gastric cancer (EGC); lymph node metastasis (LNM); clinicopathological characteristics; laparoscopic surgery

The minimalization of therapeutic invasiveness in order to preserve quality of life is a major topic in the management of early gastric cancer (EGC). After laparoscopic surgery for gastric cancer was introduced by Kitano *et al* in 1991, an enthusiasm to develop laparoscopic procedures has grown steadily [1]. This minimally invasive technique can be applied for the management of EGC without the risk of lymph node metastases (LNM) [2–5]. The application of laparoscopic surgery has been limited to differentiated EGC because of the higher risk of lymph node metastases in poorly differentiated EGC, compared to differentiated EGC [6]. Therefore, gastrectomy with lymphadenectomy has been considered to be an essential treatment for patients with poorly differentiated EGC. However, almost all (96.6%) surgical cases of poorly differentiated EGC confined to the mucosa, have been found not to have LNM [8], suggesting that gastrectomy with lymphadenectomy may be overtreatment for these cases.

Therefore, we carried out this retrospectively study to determine the clinicopathological factors that are predictive of LNM in intramucosal poorly differentiated EGC. Furthermore, we established a simple criterion to expand the possibility of using laparoscopic surgery for the treatment of intramucosal poorly differentiated EGC.

## Materials and methods

### Patients

Patients underwent a radical operation due to EGC in the Department of Oncology Surgical, Affiliated Xingtai People Hospital of Hebei Medical University (China) between January 1992 and December 2008 were included in

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the screening for identification of cases with EGC in this retrospective study.

The inclusion criteria for this study were: (1), lymph node dissection beyond limited (D1) dissection was performed; (2), the resected specimens and lymph nodes were pathologically analyzed, and poorly differentiated EGC was diagnosed, according to the Japanese Classification of Gastric Carcinoma (JCGC) [7]; and 3), patients' medical records were available in the database.

During the 16 years, 65 patients (50 male, 15 female; mean age 46 years, range 29–78 years) with histopathologically poorly differentiated type were identified to meet the inclusion criteria for further analysis in this study.

### Dissection lymph nodes and assessment and classification of LNM

Lymph nodes of each case were meticulously dissected from the enbloc specimens, and the classification of the dissected lymph nodes was determined by a surgeon after he/she who carefully reviewed the excised specimens based on the JCGC [8]. Then, the resected lymph nodes were sectioned and stained with hematoxylin and eosin and examined by pathologists for metastasis and lymphatic vessel involvement (LVI).

### Association between clinicopathological parameters and LNM

Clinicopathological parameters that are covered in the JCGC [7] were included in this study. They were the gender (male and female), age (< 60 years, ≥ 60 years), family medical history of gastric cancer, number of tumors (single or multitude), the location of the tumor (upper, middle, or lower of the stomach), tumor size (maximum dimension ≤ 2 cm, or >2 cm), macroscopic type [protruded (type I), superficial elevated (type IIa), flat (type IIb), superficial depressed (type IIc), or excavated (type III)], depth of invasion (mucosa, submucosa), LVI.

The associations between various clinicopathological factors and LNM were examined as described below.

### Statistical analysis

All data were analyzed using SPSS15.0 statistical software (USA). The differences in the clinicopathological parameters between patients with and without LNM were determined by the $\chi^2$ test. A multivariate stepwise logistic regression analysis was performed subsequently in order to identify independent risk factors for LNM. Hazard ratio and 95% confidence interval (CI) were calculated. A $P$ value of less than 0.05 was considered statistically significant.

## Results

### Association between clinicopathological factors and LNM

The association between various clinicopathological factors and LNM was first analyzed by the $\chi^2$ test (Table 1). Multitude of tumors, a tumor larger than 2.0 cm, and the presence of LVI were significantly associated with a higher rate of LNM ($P < 0.05$).

However, gender, age, family medical history of gastric cancer, location, and macroscopic type were found not to be associated with LNM.

### Multivariate analysis of potential independent risk clinicopathological factors for LNM

The three characteristics that were significantly associated with LNM by univariate analysis were found to be significant and independent risk factors for LNM by multivariate analysis ($P < 0.05$, Table 2).

### LNM in intramucosal poorly differentiated EGC

LNM was histologically confirmed in 5 (7.7%) of the 65 patients. The LNM rates were 5.0%, 18.2% and 66.7%, respectively in cases with one, two and three of the risk factors respectively in intramucosal poorly differentiated EGC. There was no LNM in 31 patients without the three risk clinicopathological factors.

## Discussion

Laparoscopic surgery has been associated with less pain, quicker return of gastrointestinal function, better pulmonary function, decreased stress response, a shorter hospital stay and better postoperative quality of life than open gastrectomy [9, 10].

The present multivariate analysis revealed that multitude of tumors, a tumor larger than 2.0 cm, and the presence of LVI were significant predictive factors for LNM in patients with intramucosal poorly differentiated EGC. Our results collaborate those of previous reports on undifferentiated EGC, which demonstrated a significant correlation between the high incidence of LNM and multitude of tumors, a tumor larger than 2.0 cm, and the presence of LVI [11–13].

We then attempted to identify a subgroup among intramucosal poorly differentiated EGC patients in whom the risk of LNM can be highly ruled out, namely candidates who can be curably treated by laparoscopic surgery. As a result, we found no LNM in patients with single of tumor if the tumor is less than or equal to 2.0 cm in size without LVI. This may indicate that laparoscopic surgery could be sufficient to treat these cases, and that additional surgery is unnecessary.

We further examined the relationship between the

**Table 1** Univariate analysis of potential risk characteristics for LNM

| Characteristic | *n* | LNM positive number | | *P* value |
|---|---|---|---|---|
| | | *n* | % | |
| Sex | | | | 0.875 |
| Male | 50 | 4 | 8.0 | |
| Female | 15 | 1 | 6.7 | |
| Age (years) | | | | 0.785 |
| < 60 | 55 | 4 | 7.3 | |
| ≥ 60 | 10 | 1 | 10.0 | |
| Family medical history | | | | 0.520 |
| Positive | 5 | 0 | – | |
| Negative | 60 | 5 | 8.3 | |
| Number of tumors | | | | 0.009 |
| Single | 61 | 3 | 4.9 | |
| Multitude | 4 | 2 | 50.0 | |
| Location | | | | 0.786 |
| Upper | 15 | 1 | 6.7 | |
| Middle | 5 | 0 | – | |
| Lower | 45 | 4 | 8.9 | |
| Tumor size in diameter (cm) | | | | 0.032 |
| ≤ 2 | 44 | 1 | 2.3 | |
| >2 | 21 | 4 | 19.0 | |
| Macroscopic type | | | | 0.750 |
| I | 3 | 0 | – | |
| II | 47 | 3 | 6.4 | |
| III | 15 | 2 | 13.3 | |
| LVI | | | | < 0.001 |
| Positive | 9 | 4 | 44.4 | |
| Negative | 56 | 1 | 1.8 | |

**Table 2** Multivariate analysis of potential risk factors for LNM

| Characteristic | Hazard ratio | 95% CI | *P* value |
|---|---|---|---|
| Tumor size (cm) | 5.245 | 1.785–45.321 | 0.039 |
| ≤ 2 | | | |
| > 2 | | | |
| Number of tumors | 25.377 | 1.971–85.134 | 0.012 |
| Mucosa | | | |
| Submucosa | | | |
| LVI | 44.112 | 1.69–112.471 | 0.014 |
| Positive | | | |
| Negative | | | |

positive number of the three significant predictive factors and the LNM rate in order to establish a simple criterion for an optimal strategy for treatment of intramucosal poorly differentiated EGC. In the present study, The LNM rates were 5.0%, 18.2% and 66.7%, respectively in cases with one, two and three of the risk factors respectively in intramucosal poorly differentiated EGC. Therefore gastrectomy with lymphadenectomy is inevitable for these patients with the risk factors.

According to our study, we would propose a treatment strategy for patients with intramucosal poorly differentiated EGC. Laparoscopic surgery alone may be sufficient treatment for single of tumor if the tumor is less than or equal to 2.0 cm in size, and when LVI is absent upon postoperative histological examination. When specimens shows with LVI, an additional gastrectomy with lymphadenectomy should be recommended.

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# Retrospective analysis of TACE times after primary liver cancer operation

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**Abstract** ***Objective:*** The aim of the study was to probe into the impacts of the times of preventive transcatheter arterial chemoembolization (TACE) after operation treatment for patients with primary liver cancer on their survival. ***Methods:*** We selected 103 patients with primary liver cancer to conduct retrospective analysis who received preventive TACE after operation treatment between 2003 and 2008 and analyzed the impact of TACE times on the patients. ***Results:*** The survival rates for 103 patients after treatment with TACE for 1 year, 2 years and 3 years were 94.17%, 65.05% and 40.78% respectively. We adopted Kaplan-Meier to analyze the survival rate. When TACE times were more than 1 time ($\chi^2 = 7.779$, $P = 0.005$; $\chi^2 = 11.806$, $P = 0.001$) and 2 times ($\chi^2 = 4.306$, $P = 0.038$; $\chi^2 = 4.769$, $P = 0.029$), they respectively had statistics significance to increase 2-year survival rate and 3-year survival rate of patients. They have no significant relevance with 1-year survival rate ($P > 0.05$). When TACE time was more than 3 times, it had not statistics significance to enhance 1-, 2- and 3-year survival rates of patients ($P > 0.05$). ***Conclusion:*** The 1–3 times of preventive TACE treatment can improve patients' survival rate in the near future.

**Key words** primary liver cancer; post-operation; intervention time; survival

Primary liver cancer is a highly malignant tumor with extremely high death rate. Surgical resection together with transcatheter arterial chemoembolization (TACE) is still regarded as an effective treatment means. However, there are few literatures and reports about whether prognosis is in direct proportion to TACE times and whether the curative effect and the survival rate of patients increase with the increase in TACE times. The author conducted statistical analysis of the relationship between the survival and TACE times for 103 patients who received TACE after post-operation of liver cancer in July, 2003 and December, 2008. The report was as follows.

## Patients and methods

### Case information

We selected the patients with surgical resection for live cancer who were diagnosed as primary liver cancer in the Affiliated Hospital of Qingdao University Medical College (China) between July 2007 to December 2008. Collected 103 patients' case information with post-operation TACE treatment for follow-up visit. The information was relatively complete, including 14 female patients, 89 male patients with the age between 22–74 years old and the average age of 55.4 years old. Eighty-three patients suffered from hepatitis B or positive hepatitis B surface antigen (HBsAg), and 20 patients with negative HBsAg. There were 203 interventions for all cases, 1 time at lest and 9 times at most, with the average times of 1.97. Fifty-five patients received 1 time treatment, 48 cases more than 1 time, 27 cases 2 times, 21 more than 2 times, 5 cases 3 times, and 16 more than 3 times. We adopted survival time as the standard to judge the curative effect.

### Therapeutic method

Adopted Seldinger method for TACE treatment after primary liver cancer operation, i.e. femoral artery puncture on right side to proper hepatic artery. According to patients' general conditions, cirrhosis degrees, tumor size, satellite nodule condition, vessel and vessel cancer embolus conditions, injected chemotherapeutics with different dosages, including 5-fluorouracil 500–1000 mg, mitomycin 8–10 mg, cis-platinum 20–80 mg and pirarubicin 30–50 mg as well as gelfoam. In terms of therapeu-

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**Table 1** Relationship between general conditions of patients and pathology composition as well as intervention times

| Variable | TACE times | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 time | > 1 time | | ≤ 2 times | > 2 times | | ≤ 3 times | > 3 times | |
| Gender | | | | | | | | | |
| Male | 46 | 43 | $\chi^2 = 0.772$ | 71 | 18 | $\chi^2 = 0.011$ | 75 | 14 | $\chi^2 = 0.019$ |
| Female | 9 | 5 | $P = 0.380$ | 11 | 3 | $P = 0.917$ | 12 | 2 | $P = 0.890$ |
| Age (years) | | | | | | | | | |
| ≤ 50 | 37 | 40 | $\chi^2 = 3.503$ | 59 | 18 | $\chi^2 = 1.678$ | 59 | 13 | $\chi^2 = 0.423$ |
| > 50 | 18 | 8 | $P = 0.061$ | 23 | 3 | $P = 0.195$ | 23 | 3 | $P = 0.515$ |
| Hepatitis | | | | | | | | | |
| Yes | 14 | 6 | $\chi^2 = 2.749$ | 19 | 1 | $\chi^2 = 3.621$ | 20 | 65 | $\chi^2 = 0.403$ |
| No | 41 | 42 | $P = 0.097$ | 63 | 20 | $P = 0.057$ | 3 | 15 | $P = 0.525$ |
| Hemangioma cavernosum embolus | | | | | | | | | |
| No | 45 | 43 | $\chi^2 = 0.242$ | 71 | 18 | $\chi^2 = 0.011$ | 76 | 13 | $\chi^2 = 0.429$ |
| Yes | 10 | 5 | $P = 0.265$ | 11 | 3 | $P = 0.917$ | 11 | 3 | $P = 0.512$ |
| Tumor size (cm) | | | | | | | | | |
| ≤ 5 | 22 | 26 | $\chi^2 = 2.067$ | 39 | 10 | $\chi^2 = 0.000$ | 39 | 9 | $\chi^2 = 0.709$ |
| > 5 | 33 | 22 | $P = 0.151$ | 43 | 11 | $P = 0.996$ | 48 | 7 | $P = 0.400$ |
| Pathology | | | | | | | | | |
| High or middle differentiated | 39 | 32 | $\chi^2 = 0.215$ | 56 | 15 | $\chi^2 = 0.770$ | 59 | 12 | $\chi^2 = 0.326$ |
| Poorly differentiated | 16 | 16 | $P = 0.643$ | 26 | 6 | $P = 0.782$ | 28 | 4 | $P = 0.568$ |
| TNM stage | | | | | | | | | |
| I | 33 | 30 | $\chi^2 = 4.079$ | 49 | 14 | $\chi^2 = 0.401$ | 53 | 10 | $\chi^2 = 0.566$ |
| II | 9 | 12 | $P = 0.130$ | 17 | 4 | $P = 0.818$ | 17 | 4 | $P = 0.753$ |
| III | 14 | 5 | | 16 | 3 | | 17 | 2 | |

tic schedule, for those whose incisal edge was not cured completely after liver cancer resection or Alpha Fetoprotein (AFP) level remained high after the operation, removed activity hepatopathy, extrahepatic recurrence or gestation and conducted one TACE within 1 month post-operation. Conducted computed tomography (CT) scanning within 20 days to 1 month after TACE operation. If there was no iodipin deposit in the liver and AFP level did not increase, it indicated that the possibility for nidus remaining in the liver was not high and TACE might not be conducted any longer. If there was sheet-shaped iodipin deposit, conducted TACE treatment for those whose liver might have nidus. For the patients with poor liver reserve function (cirrhosis, serious hepatatrophia, abnormal transaminase), TACE treatment should be based on embolism and reduced a half of chemotherapeutics so as to improve the safety in treatment.

### Observation index

Conducted follow-up visit of all patients till then end of December 2008, so there was complete follow-up visit information. Observed the impact of TACE times on post-operation of primary liver cancer. We compared 1-, 2- and 3-year survival rates after TACE.

### Statistics treatment

We adopted SPSS 17.0 statistics software package for analysis, and adopted Pearson chi-square test to analyze whether the gender, age, hepatitis, hemangioma cavernosum embolus, tumor size, tumor differentiation degree as well as tumor, nodes, metastasis-classification (TNM) (National Comprehensive Cancer Network, NCCN Version 2010) and TACE times had statistics significance. Then we used Kaplan-Meier to analyze the survival rate and the impact of Log-Rank examination single factor on the survival rate. There was statistics significance for $P \leq 0.05$.

## Results

### Survival time

The total survival rates for 1, 2 and 3 years after post-operation TACE treatment were 94.17%, 65.05% and 40.78%, respectively. The longest survival time was 76 months and the shortest one was 1 month and the median survival time was 33.29 months.

### Pearson chi-square test analysis

Table 1 showed relationships between TACE times and the gender, age, hepatitis, hemangioma cavernosum embolus, tumor size, tumor differentiation degree as well as TNM staging of patients in each group. General condition of patients in various groups and pathology composition differences had no statistics significance ($P > 0.05$). The 1-, 2- and 3-year survival rates among each group were of comparability.

**Table 2** Relationship between TACE times and the survival rate of patients with liver cancer after TACE operation

| Times (cases) | Survival rate | | | | | |
|---|---|---|---|---|---|---|
| | 1-year (%) | | 2-year (%) | | 3-year (%) | |
| = 1 time (55) | 90.91 | $\chi^2 = 1.519$, $P = 0.218$ | 52.73 | $\chi^2 = 7.779$, $P = 0.005$ | 25.45 | $\chi^2 = 11.806$, $P = 0.001$ |
| > 1 time (48) | 97.92 | | 79.17 | | 58.33 | |
| ≤ 2 times (82) | 100.00 | $\chi^2 = 0.001$, $P = 0.970$ | 74.07 | $\chi^2 = 4.306$, $P = 0.038$ | 55.56 | $\chi^2 = 4.769$, $P = 0.029$ |
| > 2 times (21) | 95.24 | | 85.71 | | 61.90 | |
| ≤ 3 times (87) | 100.00 | $\chi^2 = 0.070$, $P = 0.792$ | 100.00 | $\chi^2 = 1.873$, $P = 0.171$ | 60.00 | $\chi^2 = 2.996$, $P = 0.830$ |
| > 3 times (16) | 93.75 | | 81.25 | | 62.50 | |

## The survival rate analysis by Kaplan-Meier method

The 1-, 2- and 3-year survival rates of patients with 1 time of TACE were 90.91%, 52.73% and 25.45% respectively; the 1-, 2- and 3-year survival rates of patients with more than 1 time of TACE were 97.92%, 79.17% and 58.33% respectively. The 1-, 2- and 3-year survival rates of patients with 2 times of TACE were 100%, 74.07% and 55.56% respectively; the 1-, 2- and 3-year survival rates of patients with more than 2 times of TACE were 95.24%, 85.71% and 61.90% respectively. The 1-, 2- and 3-year survival rates of patients with 3 times of TACE were 100%, 100% and 60.00% respectively; the 1-, 2- and 3-year survival rates of patients with over 3 times of TACE were 93.75%, 81.25% and 62.50%, respectively. When TACE times were more than 1 time ($\chi^2 = 7.779$, $P = 0.005$; $\chi^2 = 11.806$, $P = 0.001$) and 2 times ($\chi^2 = 4.306$, $P = 0.038$; $\chi^2 = 4.769$, $P = 0.029$), they respectively had statistics significances to increase 2-year survival rate and 3-year survival rate of patients. We adopted Kaplan-Meier for analysis and the survival rates of each group and their differences were shown in Table 2 and Fig. 1–4.

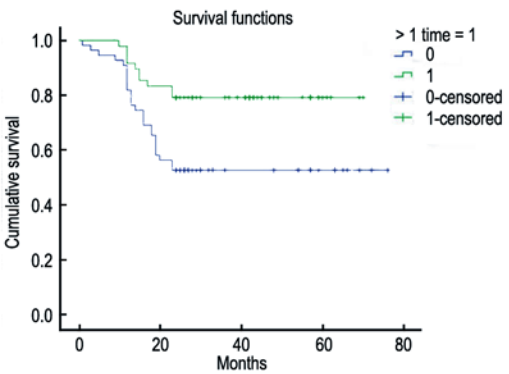


**Fig. 1** The 2-year survival rates curves of patients with more than 1 time of TACE

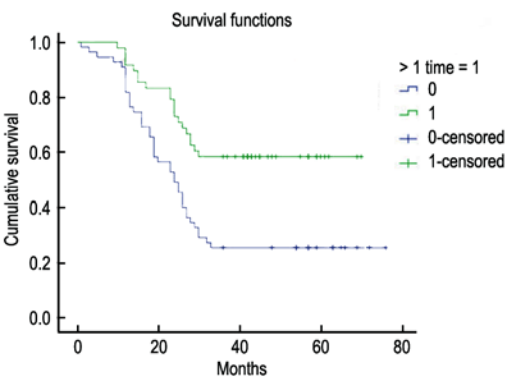


**Fig. 2** The 3-year survival rates curves of patients with more than 1 time of TACE

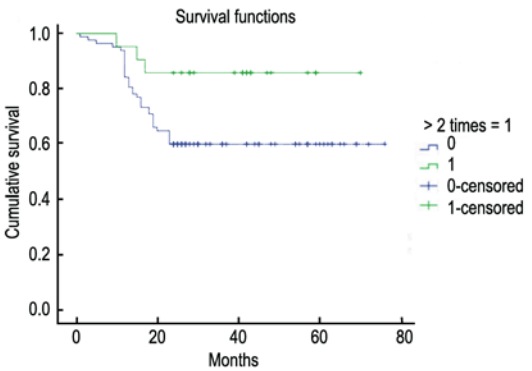


**Fig. 3** The 2-year survival rates curves of patients with more than 2 times of TACE

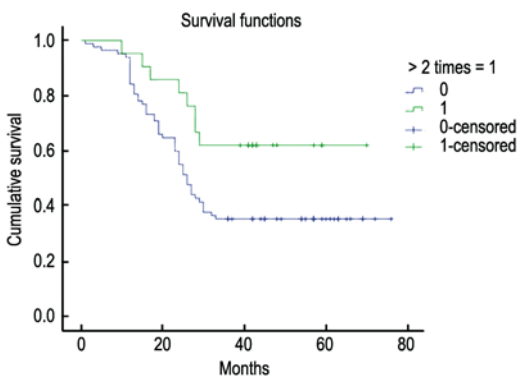


**Fig. 4** The 3-year survival rates curves of patients with more than 2 times of TACE

## Discussion

Post-operation palindromia for primary liver cancer is one of main causes to affect patients' survival time. How to reduce palindromia is the key to further improvement of the curative effect. The fastigium for liver cancer palindromia occurs within 2 years after the operation which is also the best time to prevent and cure the palindromia [1]. Post-operation palindromia in early stage is related to biological characteristics of the tumor, while palindromia in later stage is related to patients' general conditions [2, 3]. Wang *et al* [4] considered AFP level of pre-operation serum, tumor size, number of tumors, differentiation degree and hemangioma cavernosum embolus are important factors to affect post-operation palindromia in early stage. These factors reflect biological characteristics of the tumor. It is reported in literatures that for the patients with liver cancer after radical resection, the recurrence rate is as high as 60% in 5 years, and the recurrence rate with small live cancer radical resection is also as high as over 40%. In addition, the recurrence time mainly concentrates on about 2 years after the operation [2, 3]. At present, TACE method is mainly adopted for preventive treatment for liver cancer post-operation, but the curative effect has disputes. Each report is not all the same, but most scholars consider post-operation TACE can improve the survival rate of patients [5]. However, there are relatively few research literatures about the relationship between TACE times after liver cancer operation and patients' prognosis.

We divided 103 patients with different intervention times after liver cancer operation into 3 groups: equal to 1 time and over 1 time groups, less than or equal to 2 times and more than 2 times groups, less than or equal to 3 times and more than 3 times groups. We adopted Pearson chi-square test to analyze the gender, age, hepatitis, hemangioma cavernosum embolus, tumor size, tumor differentiation degree as well as TNM staging of patients in each group. The result showed that general conditions of patients in each group and pathology composition differences have no statistics significances ($P > 0.05$), i.e. 1-, 2- and 3-year survival rates in each group have comparability. Then we adopted Kaplan-Meier analysis to compare the survival rates of each group and the result showed as follows: in equal to 1 time and over 1 time group and less than or equal to 2 times and more than 2 times group, there was no obvious impact on 1-year survival rate of patients, but there was significances for 2-year and 3-year survival rates of patients, i.e. improving patients' survival rate; for patients in less than or equal to 3 times and more than 3 times group, there was no significance for 1-, 2- and 3-year survival rates ($P > 0.05$).

The main effect of TACE after liver cancer operation lies in blocking blood supply of tiny focal cancer, controlling tiny nidus which is not removed completely through operation by use of a small quantity of iodipin together with anti-cancer drugs so as to reach the effect to prevent recurrence. In addition, it can find and cure residual cancer and nidus recurrence in time and complete early treatment. It is effective to improve patients' survival rate for 1 to 3 times of TACE treatment. However, TACE treatment is a "double-edged sword". It causes huge harm to organism while killing tumor cells, especially harmful to liver functions. The harm degree is in direct proportion to times of TACE treatment, i.e. more times of TACE, higher damage degree to liver functions is. After 3 times of TACE treatment, it is found that the vessel of embolism part is locked and that embolism chemotherapeutics cannot accumulate so that the treatment purpose is not achieved [4]. Meanwhile, repeated TACE treatment may aggravate the degree of liver fibrosis, which seriously affects liver functions [6]. Zhang *et al* [7] also reported that although treatment time is related to the survival rate after TACE operation, it is not enough to affect independent factors of prognosis. This may result from that the formation of tumor collateral circulation after TACE operation, production of multiple drug resistance as well as multiple TACE treatment inevitably harm liver functions. The study shows that angiogenesis of residual cancer tissue of hepatic cell cancer after TACE treatment increases. When tumor cells lack blood and oxygen, more angiogenesis promotion factors are produced. Most important of all, vascular endothelial growth factor (VEGF) increases and collateral circulation is formed [8, 9]. In addition, liver cancer post-operation intervention treatment cannot prevent focal cancer occurring in multi-centers. This also shows that in clinical practices, it is necessary to decide times of TACE treatment and time interval according to specific status of patients' liver functions and iodized oil deposit in the tumor.

In accordance with this result, we consider proper TACE treatment after liver cancer operation has relatively high clinical value, but its application scope should not be expanded blindly. It is required to master intervention indication strictly. It is of extremely important clinical significance to protect liver functions, maintain patients' good living level and reduce unnecessary pains. Repeated preventive TACE after liver cancer operation cannot improve anti-recurrence effect of TACE. Therefore, we do not advocate more than 3 times of preventive TACE treatment.

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# The clinical observation of three-dimensional conformal radiotherapy combined with FOLFOX chemotherapy for rectal cancer of postoperative local recurrence

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**Abstract** ***Objective:*** The aim of this study was to explore the three-dimensional conformal radiotherapy combined with FOLFOX scheme chemotherapy in the treatment of postoperative recurrence of rectal cancer. ***Methods:*** Sixty-eight cases of recurrent rectal cancer were divided randomly into two groups: 34 cases of conformal radiotherapy plus FOLFOX chemotherapy group (experiment group) and 34 cases of conformal radiotherapy (control group). After 6 MvX line with three-dimensional conformal radiotherapy technologies for recurrent lesions and pelvic cavity around subclinical lymphatic drainage radiotherapy after radiotherapy to DT 40 Gy to reposit was made use of between both groups, experiment group was made the new treatment plan to continue to irradiate to 50 Gy, and then Shrinkage GTV was pushed quantity in the field 66 Gy. Researchers took chemotherapy in the first week and the fourth week after radiotherapy, with 5-fluorouracil 500 mg/m$^2$, calcium leucovorin 200 mg, d1–5 with intravenous drip, Oxaliplatin 130 mg/m$^2$ and d1 with intravenous drip 2 h, 21 days was one cycle. Kaplan-Meier method was used for survival analysis. ***Results:*** The survival rates for 1, 2 and 3 years for experiment group and control group were 88.2%, 64.7%, 47.1% and 66.7%, 38.2%, 29.4% ($P$ = 0.03), the 2-year rate of distant metastases was 32.4% and 58.8% ($P$ = 0.032) respectively. The median survival time was 33 and 20 months respectively. There were some side effects between the groups, but there was no statistical difference. ***Conclusion:*** Three-dimensional conformal radiotherapy plus FOLFOX chemotherapy can be considered as a safe and effective approach to treat rectal cancer patients of postoperative recurrence, and can improve the survival rates of patients and reduce distant metastasis rate obviously and make the acute adverse reaction rate insignificantly.

**Key words** rectal neoplasm; tumor recurrence; conformal radiotherapy; chemotherapy

The rectal cancer is one of common malignant tumors, and the surgery is the preferred treatment. However, the rectal cancer has a higher recurrence rate after the surgery. Most of the recurrent disease has no possibility to operate, and the main comprehensive treatment is the radiotherapy. The three-dimensional conformal radiotherapy (3DCRT) is a treatment technology that enables the shape in the high-dose region to consist with the shape of lesions 3-dimensionally, and the recurrence of the rectal cancer after the 3DCRT can reduce the digestive tract and urinary tract reactions caused by the radiation therapy. In order to discuss the postoperative efficacy of the FOLFOX chemotherapy to the rectal cancer recurrence, we adopt the 3DCRT technology program combined with the FOLFOX chemotherapy (experimental group) and the single radiotherapy (control group) for treatment of 68 cases of the rectal cancer recurrence.

## Materials and methods

### Clinical data

We had 68 patients with the rectal cancer recurrences after the resection from January, 2005 to December, 2007. There wass no distant metastasis; the Karnofsky score was > 70; there was no other serious illness; all the cases were the rectal cancer recurrences; and there was no radiotherapy and the patients were reluctant to accept the surgery. There were 42 male patients and 26 female patients and the medium age was 57 years old (27 to 72 years old). Moreover, there were 39 tubular adenocarcinoma cases and 29 mucinous adenocarcinoma cases. The clinical data was shown in Table 1.

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**Table 1** The clinical data of the 68 cases of rectal cancer recurrence

| | Experiment group | Control group |
|---|---|---|
| Total cases | 34 | 34 |
| Medium age (years) | 45 | 50 |
| The maximum tumor diameter (cm) | 2–7 | 3–6 |
| Surgical way | | |
| Mile | 18 | 20 |
| Dixon | 16 | 14 |
| Pathological type | | |
| Mucinous adenocarcinoma | 21 | 18 |
| Tubular adenocarcinoma | 13 | 16 |

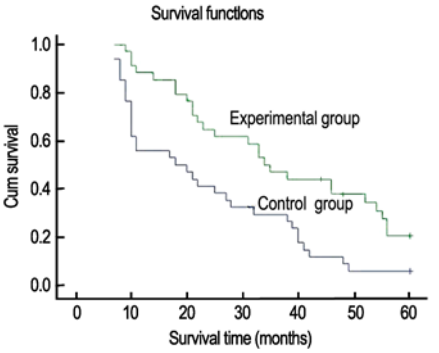


**Fig. 1** The survival graph comparison of experiment group and control group

### Treatment methods

Experimental group and control group all used the 6 MvX line for the full three-dimensional conformal radiotherapy, which adopted the stereotactic body frame and three-dimensional radiotherapy treatment planning system (TPS) produced by Shanghai TOPSLANE Technolage Company (China). Tell the patients to drink the 20 mL compound diatrizoate added with 500 mL normal saline to ensure the filling bladder, and the Miles patients would be tagged at the perineal surgery scars. The patients should lie in the supine shape on the stereotactic shelves of the CT simulator, with his two hands on the forehead, using the negative pressure vacuum pad to fix the chest, abdomen and pelvis of the patient, using the spiral CT to enhance scan, and the scan range was the pelvic cavity and abdomen with the thickness of 5 mm. The scan data was transmitted over the network to the three-dimensional treatment planning system. The target region was outlined by the competent physician and the CT Diagnosis physician. The gross tumor volume (GTV) included the recurrence focus, clinical target volume (CTV): including the rectum around the membrane area, the presacral area, the external iliac vessels and part of the common iliac vessels on the upper edge of the sacral 3, all the lymph nodes drainage areas around the iliac vessels, the perineal surgical scar (Miles surgery) and the ischial rectal fossa. The planning target volume (PTV) expanded 0.5 cm of the CTV basis, and expands 1.0 cm on the direction of belly, back, foot and leg. Adopting one center and 4 to 6 portal irradiation, and 90% isodose to surround the PTV, and the internal difference of the PTV dose wass best for within ± 5%. Notice the limited requirements of the bladder, the femoral head, uterus, small intestine and other important parts. The split dose was 2 Gy/times, and 5 times/week. Do the pelvic CT after a total dose of 40 Gy, and continued to exposure to 50 Gy, then reducing the wild shot of the GTV to 66 Gy. The patients in experimental group all do the chemotherapy in the first and fourth week, using 5-fluorouracil (5-FU) 500 mg/m$^2$, folinic CF 200 mg, and d1–5 to infuse intravenously, the oxaliplatin 130 mg/m$^2$, d1, intravenous infusion 2 h, and repeated in every 21 days. The chemotherapy cycle was 2 weeks. control group did not undergo the chemotherapy. At the end of the radiotherapy, the patients could rest for 3 to 4 weeks, then doing the FOLFOX adjuvant chemotherapy with 4 cycles.

### Statistical analysis

Use the SPSS13.0 package and Kaplan-Meier to conduct the survival analysis, and the Longrank line difference test. Then, use the $\chi^2$ to test the count data, and the order sum to test the grade data.

### Criteria to determine the efficacy

According to the efficacy of the WHO solid tumor, the evaluation criteria can be divided into complete remission (CR), partial remission (PR), stable (SD), progress (PD), and CR + PR was effective. The efficacy was evaluated by the CT or MRI in the three months after the treatment. The normal tissue acute reaction was evaluated according to the RTOG evaluation standard.

## Results

### Follow-up

All patients were followed up to December 2010, and the follow-up rate was 97.1%.

### Recent efficacy

The pain relief rate of experimental group and control group were 94.1% (32/34) and 88.2% (30/34), respectively, and the difference was not significant ($P = 0.393$). The tumor efficiency (CR + PR) of experimental group and control group were 91.2% (31/34) and 70.6% (24/34), respectively, and the difference was significant ($P = 0.031$).

### Survival rate

The survival rates of experimental group and control group in the 1, 2, 3 year were 88.2%, 64.7%, 47.1% and 67.7%, 38.2%, 29.4%, and the median survival cycle was 33 and 20 months. The survival rate of experimental group was higher than that of control group, and had sig-

**Table 2** Side effects after treatment (*n*, %)

| Groups | Radiation cystitis | | | | Radiation proctitis | | | | Dccreased white blood cell | | | | Gastrointestinal tract effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | I | II | III | IV | I | II | III | IV | I | II | III | IV | I | II | III | IV |
| Experiment group | 7 | 5 | 0 | 0 | 9 | 6 | 0 | 0 | 13 | 9 | 5 | 1 | 12 | 9 | 2 | 0 |
| Control group | 8 | 9 | 0 | 0 | 10 | 7 | 0 | 0 | 11 | 8 | 4 | 0 | 9 | 7 | 1 | 0 |
| *P* | 0.557 | | | | 0.947 | | | | 0.798 | | | | 0.902 | | | |

nificant statistic difference ($P = 0.03$; Fig. 1).

### The distant metastasis rate in two years

The distant metastasis rate of experimental group and control group was 32.4% and 58.8% respectively in two years. The distant metastasis rate of experimental group in two years was lower than that of control group ($P = 0.032$).

### Treatment response

All the patients had completed the treatment successfully. The bone marrow suppression, gastrointestinal reactions, radioactive radiation proctitis and cystitis were the main poisoning reactions. Refer to Table 3. There was no statistic difference of the comparison between two groups (Table 2).

## Discussion

Although the surgical techniques are improving, the local recurrence after the surgery is still the main reason for treatment failure in the rectal cancer. The local recurrence rate of the rectal cancer after the surgery of the T1–2N0M0 rectal cancer is less than 10%, while the recurrence rate of the T3N0M0 has risen to 15–35%, and the recurrence rate of T3–4N1–2M0 is as high as 45 to 65% [1]. Due to most of the local recurrences are in the pelvic cavity, the tumor invasion or compression will cause pain in the surrounding area. The most common symptoms of patients are the perineal or sacral pain, a sense of falling, sometimes with lower limb pain and blood in the stool, and more secretions, etc. Some patients have hard and fixed mass in the perineum. Focus on these kinds of patients to conduct the integrated radioactive treatment can reduce pain. In this paper, the pain relief rates in experimental group and control group are 94.1% and 88.2%, which improve the life quality of the patients.

For the rectal cancer patients with local recurrence after surgery, it is difficult to conduct the resection again, and the complications are high. In the mid 90's, some scholars have adopted the aggressive surgical approach to the patients, such as using the resection of all pelvic cavity surgery, and the abdominal sacral resection surgery, but the local recurrence rate for the second surgery is as high as 77%, which shows that the wide spread in the pelvic cavity can not achieve the purpose of removing the primary tumor totally by surgery [2]. Therefore, the surgical resection is not the main treatment to the recurrence patients, and most of them need to be cured by comprehensive treatment. The chemotherapy alone for the rectal cancer is not superior to radiotherapy or the chemotherapy and radiotherapy together [3]. Yang Xiaobin *et al* reported [4] that the first postoperative TNM staging, recurrence region, time to relapse and the treatment way after recurrence are the independent prognostic factor of the local recurrence of rectal cancer, the integrated radiotherapy and chemotherapy could enable the patients to live. Studies have shown that conduct the integrated radiotherapy and chemotherapy could reduce the rate of local recurrence and distant metastasis, and improve the survival rate. To conduct the integrated radiotherapy and chemotherapy 5-FU-based plan after the radical surgery for rectal cancer is the conventional radiotherapy treatment [5, 6]. The integrated radiotherapy and chemotherapy could change the fate of the rectal cancer recurrence patients, and could have the function of improving efficiency, increasing sensitivity, and complementing mutually. 5-FU is still one of the important drugs to cure the advanced colorectal cancer, and the 5-FU/LV as the standard program of colorectal cancer has been used in the clinical practice for more than ten years. Oxaliplatin is a novel derivative of the cisplatin, belongs to the 3rd generation platinum anticancer drugs, with the mechanism by producing alkyl compounds to act on DNA, and combining with the C covalent bond on the DNA chain, forming the internal and cross-linking chain, and the protein chain, thus inhibiting DNA synthesis and replication, causing cell toxicity, and cell death [7]. The side effects of it are less, and has synergistic effect with 5-FU, and has shown a high degree of antitumor activity in the phase III trials of advanced colorectal cancer. Studies of the phase III trials have shown that the oxaliplatin added 5-FU/LV can release more than 5-FU/LV alone, and have longer TTP, and is considered as the new standard program for the colorectal cancer treatment [8, 9]. A large number of clinical practices have proved that the FOLFOX series of programs have advantages in treating the advanced colorectal cancer compared with the 5-FU + LV treatment. The "New England Journal of Medicine" in 2004 reported in detail [10] that the patients with colorectal cancer after the surgery who conduct the FOLFOX group adjuvant therapy have the disease-free survival rate was 77.9% in 3 years, while the LV/5-FU group was 72.8% ($P < 0.01$). Therefore, in this article the test adopts the FOLFOX as

the synchronous chemotherapy drugs, conducts the radiation therapy in the first or the fourth week respectively, and has not significantly increased radiation toxicity. The bone marrow suppression and gastrointestinal reaction probability is similar in experimental group and control group, and both of the two groups are not interrupted or delayed in treatment due to the acute toxicity. The local recurrences of rectal cancer are mainly of the recurrences of the primary tumor bed and pelvic lymph node. The conventional radiotherapy can not only improve tumor dose, but also increase the normal dose of the rectum and bladder, and increase the incidence of the radioactivity cystitis and proctitis, and this is one of the main reasons for the limited pelvic radiation dose. The 3DCRT is concentrating radiation to the tumor tissue by the coplanar or non-coplanar incoming direction, to let the radiation dose consistent with the target section in the three dimensions direction. When the tumor gets high dose, it can protect the surrounding normal tissue in maximum so to create the conditions for the incremental target. It shows that 3DCRT technology has obvious advantages in the protection of normal tissue than conventional radiotherapy in rectal cancer [11]. In this paper, the test of both groups all take the 3DCRT to treat, and the results have showed that the survival rate in the 1, 2, 3 year of experimental group is higher than control group which is similar with the literature [12, 13]. The toxicity reaction of the radioactivity cystitis and proctitis has no statistical difference in two groups. The distant metastasis rate of the two groups in two years is 32.4% and 48.8% respectively, which indicates that the synchronous FOLFOX chemotherapy can improve survival rate, and reduce the distant metastasis rate.

In summary, the 3DCRT combined with the synchronous FOLFOX chemotherapy is an effective treatment to cure the rectal cancer recurrence after treatment and can relieve symptoms, improve the recent survival rate, and reduce distant metastasis rate. However, the cases being not more and the follow-up time being shorter, the advantageous role of 3DCRT integrated chemotherapy in the rectal cancer radiotherapy still needs to be proven by much more cases and the longer-term follow-up.

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# The effect of anti-CD28 on the CD3-AK proliferation and tumoricidal activity

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**Abstract** ***Objective:*** The aim of this study was to costimulate the CD3-AK cells with anti-CD28 monoclonal antibody (mAb), observe the effect of cell proliferation and cytotoxicity and explore the regulatory role of CD28 mAb on the CD3-AK tumoricidal activity. ***Methods:*** To prepare CD3-AK cells, observe the number and morphology of the activated T cells with the inverted microscope and detect the inhibitory rate of the myeloma cells by methylthiazolyldiphenyl-tetrazolium bromide (MTT). ***Results:*** Adding the anti-CD28 mAb to the CD3-AK cells, the number of cells increased significantly ($P < 0.05$) and the cytotoxic activity of the cells was significantly higher ($P < 0.05$). ***Conclusion:*** The addition of anti-CD28 mAb has a strong synergistic effect, which can effectively enhance the tumoricidal activity of CD3-AK.

**Key words** CD28; monoclonal antibody (mAb); CD3-AK; myeloma cell

Anti-CD3 monoclonal antibody activated killer cells (CD3-AK cells) have strong expansion ability, long survival time *in vitro*, high cytotoxic activity and well tumoricidal effect, which can be commonly used as one of the effector cells in the clinical anti-tumor passive immunotherapy [1, 2]. CD28 is the glycoprotein molecules on the surface of T cells, its main biological effect is interaction with the natural ligands B7-1/B7-2 on the antigen presenting cell (APC), to enhance the production and secretion of IL-2, to promote T lymphocyte proliferation and activation, which is considered one of the most important T cells costimulating molecular [3, 4]. Our study used anti-CD28 monoclonal antibody to stimulate CD3-AK cells, observe the cell proliferation, cytotoxic effects and tumoricidal activity.

## Materials and methods

### Main reagents

Anti-CD28 monoclonal antibody prepared by our lab (Central Laboratory, The Military General Hospital of Beijing PLA, China); anti-CD3 monoclonal antibody (mAb) bought from HuaMei biological engineering company (China); RPMI 1640 and MTT, from Sigma (USA); IL-2 (JiLin pharmaceutical product) bought from Beijing chemical reagent company (China); SP2/0 myeloma cells from Cell Department of Beijing Hospital (China).

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### Methods

*Preparation of anti-CD28 monoclonal antibody*

Initially BALB/c mice (6 weeks old) were immunized with CD28 in complete Freund's adjuvant (CFA) and four subsequent doses were injected with incomplete Freund's adjuvant (IFA) at 14 day intervals. Antibody titers were determined by ELISA. Final booster dose was delivered by injecting antigen directly into the mice spleen. Sensitized spleen cells were fused with mouse myeloma cell line (SP2/0) using polyethylene glycol 4000 after three days from the final booster dose. Fusion cells were cloned, screened by indirect ELISA and subcloned by limiting dilution assay, hybridoma cells were obtained. These hybridoma cell lines which could secret anti-SEA monoclonal antibodies stably were inoculated into Balb/c mice sensitized with liquid paraffin to prepare ascites. Anti-CD28 monoclonal antibody was purified from the ascites.

*Production of CD3-AK cells*

The healthy donor whole blood was collected into heparinized vacutainer tubes. Peripheral blood mononuclear cell (PBMC) was separated by Ficoll density gradient centrifugation, washed with Hanks solution for three times, adjusted to $5 \times 10^5$, planted to 24-well cell culture plate with anti-CD3 (2 μg/mL) and IL-2 (100 IU/mL), 2 mL per well. The study was divided into two groups: group A as the control group; group B as the test group, adding anti-CD28 (1 μg/mL), 50 mL each well. Culturing in 37 ℃, 5% $CO_2$ incubator, change half culture medium by d2–3,

**Table 1** Counting the CD3-AK cell in different culture time

| | Cell counting (cells/mL) | | | |
|---|---|---|---|---|
| | d7 | d10 | d14 | d18 |
| Group A | $(2.4 \pm 0.3) \times 10^7$ | $(3.3 \pm 0.4) \times 10^8$ | $(8.1 \pm 0.6) \times 10^9$ | $(8.5 \pm 0.7) \times 10^9$ |
| Group B | $(2.6 \pm 0.4) \times 10^8$ | $(8.2 \pm 0.9) \times 10^9$ | $(8.7 \pm 0.7) \times 10^{10}$ | $(8.9 \pm 0.6) \times 10^{10}$ |

adding 100 IU/mL IL-2.

*Observation the effect of anti-CD28 on the CD3-AK cell proliferation*

At the different culture time (d7, d10, d15, d18), the cells proliferation were studied. Cells in 3 wells were collected from group A or B, counting cell number and observing the cell morphology by Wright Stain.

### Regulation of anti-CD28 acting on the tumoricidal activity of CD3-AK

When CD3-AK cells were cultivated to $1 \times 10^8$, SP2/0 myeloma cells were added $1 \times 10^6$ per well. After incubating for 3 days, MTT solution was added 200 μL each well. After incubating for 6 h, adding dimethyl sulfoxide (DMSO) 200 μL/well, pipetting 200 μL to 96 well microtiter plate, measured A value at 570 nm wavelength.

## Results

### Preparation of anti-CD28 monoclonal antibody

Nine anti-CD28 mAb cell lines were obtained, named as A1, A2, A3, A4, A5, A6, A7, A8, A9, four strains (A2, A3, A4, A8) of them belonged to IgG2a, 5 strains (A1, A5, A6, A7, A9) to IgG2b. The titers of the anti-CD28 mAbs were determined, which were $1 \times 10^7$ (A2), $2 \times 10^6$ (A1, A3, A4, A8), $3.2 \times 10^4$ (A5, A6, A7, A9) respectively.

### Effect of anti-CD28 on the CD3-AK cell proliferation

On the d7, d10, d14, d18, taking 20 μL of cell suspension to count the cell number. The results (Table 1) showed that cell number in group B were significantly more than group A ($P < 0.05$).

The cell morphology was observed by inverted microscope. By the d4, there was scattered small colony in the two groups, the cell number increased obviously. By the d10, there was a large number of cell clusters, the cell number in group B was significantly more than group A.

### Regulation of anti-CD28 on CD3-AK tumoricidal effect

On the d10, SP2/0 myeloma cells were added to the cultured CD3-AK cells. After 3 days, the form of cells changed, appearing an irregular and blurry cell membrane edge. The mortality rate was detected by Trypan blue staining, which was 38.3 ± 4.6 % for group A, 52.73 ± 5.2 % for group B, group B was significantly higher than group A. The inhibitory rate was determined by MTT, the results showed there was a significant difference between the two groups, group A 44.53 ± 3.9%, group B 59.53 ± 6.0 % ($P < 0.05$).

## Discussion

The biological therapy has become one of the most important means of cancer treatment, usually anti-CD3 antibodies were used to active T lymphocytes *in vitro*, $CD8^+$ $CD25^+$ T killer lymphocytes were infused to patients for therapy. T cell activation requires the first signal by the TCR/CD3 recognizing major histocompability complex (MHC)-complex peptide on the surface of the antigen presenting cell (APC) and the second signal provided by the CD28/B7 costimulating molecular. While body loaded with tumor, the specific T cells are immune tolerance, anti-CD28 can reverse T cells tolerance and arouse their antitumor activity *in vitro* and *in vivo* [5]. In recent years, researches show that anti-CD3 combined with anti-CD28 costimulating the T cells can amplify the specific CTL, augment the expression of co-stimulating molecules, and enhance T lymphocytes immune activity [6].

In this paper, we used synthetical CD28 to immunize the Balb/c mice, prepared the anti-CD28 monoclonal antibodies, and researched its effect on the T lymphocyte activation and proliferation. Results showed that anti-CD28 antibody alone couldn't stimulate the lymphocyte proliferation, which required anti-CD3 and IL-2 together. CD3-AK cells stimulated by anti-CD3 antibodies and IL-2 T cells as the control group, co-stimulated by anti-CD28 antibodies as the test group, observing the proliferation effect, the results showed the effect of the test group is obviously superior to that of the control group, suggested that there might be a certain synergy effect. In order to study tumoricidal effect, we used myeloma cells SP2/0 as the target cells. Considering the faster proliferation of myeloma cells, we chose the anti-target ratio 100: 1. After incubated 48 h, cell form did not change significantly. After 72 h, there appeared particles in the cytoplasm, individual cells had broken phenomenon, growth of the tumor cell was restrained. The inhibitory effect of the test group was obviously superior to that of the control group.

Therefore, we used anti-CD28 monoclonal antibody to imitate the co-stimulating factor *in vitro*, investigated its potential effect on the signal transduction mechanism of T cell activation and proliferation.

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# Assessment of the psychological distress difficulties in patients with cancer using the national comprehensive cancer network rapid screening measure

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**Abstract** ***Objective:*** Clinical guidelines like National Comprehensive Cancer Network Disease recommend routine psychological distress screening as a common problem among patients with cancer. The purpose of this study was to assess the prevalence of clinically significant emotional distress related to demographic and clinical association by standard distress thermometer (DT) within the patients lived in different regions of Gilan state, Iran. ***Methods:*** Participants ($n$ = 256) completed the DT, rapid screening measure for distress and identified the presence or absence of 34 problems using the standardized checklist. ***Results:*** More than 59 percent of participants had more than 4 cut-off score for distress. The scores varied significantly in case of reported emotional source of distress, physical, physiological and total number of concerns ($P$ < 0.001). DT scores more than four were more likely to report 22 of 32 problems on the problem list. In case of the practical and family problems, the main problems were related to child care and dealing with children, respectively. Moreover worrisome and nervousness were considered the prominent emotional problems in the list. ***Conclusion:*** Our result promise that distress thermometer measurement tool compare favorably with longer measures used to screening of distress in cancerous patients. Accompaniment of a psychologist expert in lethal or chronic disease consultation with the therapeutic team and training the rest of members of the team might be able to decrease the emotional distress problems of the cancerous patients.

**Key words** distress; screening; distress thermometer; malignant diseases

The patients who diagnosed with cancer, commonly experience high level of distress despite of advances in cancer therapeutic methods and treatments [1]. Social and physiological distress difficulties [2, 3] are the most common concerns in patients with cancer, but it is less clear whether these are related to cancer diagnosis. The National Comprehensive Cancer Network (NCCN) Distress Management Panel has defined this distress as "multi determined unpleasant experience of psychological (cognitive, behavioral, emotional), social, and spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and its treatment" [4]. Therefore as a routine care, NCCN recommend regular screening of all patients with cancer for psychological distress [5]. The NCCN recommendation is based on documentation that indicates clinically significant distress among cancer patients [6–8]. A wide promising point is that the most reported distress in these patients reflects longstanding issues and indirect circumstances to its cancer diagnosis and treatment. Consequently evaluation of emotional problems related to psychological symptoms by different severity [9] is important part of medical management of the cancerous patients. For best management of emotional distress in cancer patients, more data about geographical distribution of the patients, demographic and clinical association in large samples is needed. Therefore the aim of present study was to assess the prevalence of clinically significant emotional distress related to demographic and clinical association by standard distress thermometer in cancerous patients that lived in different regions of Gilan state, Iran.

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## Patients and methods

### Patients sample

All 256 individuals were a convince sample of patients diagnosed with cancer followed by pathology confirmation. The inclusion criteria for this study were as follows: diagnosis of cancer, 18 years old or older, ability to speak and communicate in Persian. The patients with brain tumors, psychiatric disorders and with neuro-psycho therapy needs were excluded from the study. All the patients were enrolled this study referred to Razi clinical and educational center, Rasht, Gilan state, Iran.

### Assessment procedure

Demographic information and medical data of our studied participants were collected using pre-designed self-report questionnaire. Data included age, gender, marital status, education, cancer type, ethnicity (center, east, west and out of state area) and annual household. Addiction and therapeutic method in the last month were received by this self report. Ethical approval was given in all study participants for data to be collected from their medical notes. These data consisted of age, postcode, gender, diagnosis, date of diagnosis, stage of disease and their family and emotional concerns. The NCCN's Distress Thermometer (DT) was administrated to measure self reported level of distress and cancer-related concerns of the sample [10]. DT is a visual analog scale, in which participants rated their level of distress from 0 (none) to 10 (extreme) in the last seven days. In this questionnaire, a cut-off point scores more than 4 indicated distresse. In addition DT cut-off score of four, assessed in present study due to its optimal sensitivity and specificity in a general cancer population relative to established cutoff scores on longer measures [11].

Also distress management guideline panel of NCCN had prepared a list with 34 common problems that cancer patients face them [5]. This list contained six categories; family, emotional problems, physical, physiological problems and spiritual/religious and practical concerns.

### Statistical analysis

SPSS for Windows, version 16 (SPSS Inc., Chicago, IL, USA) was used for all statistical procedures. Data were expressed at mean ± SD. Also data are presented in numerical form, with the results shown mostly in numerical ones or mean and percentage values. Differences in proportions were judged by $\chi^2$ test and student *t*-tests to look at differences between participants with high (DT > 4) and low distress (DT < 4). A two-tailed *P*-value less than 0.05 was considered statistically significant.

## Results

### Demographic and clinical characteristics

As presented in Table 1, 265 participants included in this study and average of their age was 53.98 years old and ranged between 18–90 years. Average of duration of cancer diagnosis was 6.79 month with minimum of one month till 5 years at maximum. Our participants included 62.1% female and 37.9% male. The majorities of the patients were married (79.3%) and lived in center of province of Gilan, in north of Iran (56.2%). About the education level, most of the participants were at primary school (37.5%) or semi-illiterate (34.4%). Sixty percent of the sample reported a monthly household income more than 1.500.000 IR-Rial. Most of our studied individuals hadn't abused cigarette (80.1%) or opium (91.4%). We recorded variety range of cancer diagnosis, with non metastatic diagnosis comprising in 94.5% of samples. The most common cancer was breast cancer (32%) then upper gastrointestinal cancer (15.6%) and then the other cancers were fairly even among the participants. Seventy two percent of participants had received only radiotherapy for their treatment in the past month, with > 19% of sample underwent both radiotherapy and chemotherapy in the same duration.

### Distress and items of concern

The distress intensity scores reported in participants of this study were as follow: 40.6% low (0–3), 42.5% moderate (4–6), and 16.9% high (7–10) (Table 2). Our analysis showed that our studied individuals split fairly between two groups; DT more than 4 (59.4%) and lower than 4 (40.6%). Chi-square analysis (Table 3) was conducted to explore the relation of DT cut-off score of less or more 4 to demographic and some clinical variables. Among measured variables, DT cut-off score only was related significantly to marital status ($P = 0.003$), with married women that experienced higher scores above cut-off score. Of the clinical variables measured, DT cut-off score was related significantly only to diagnosis of carcinoma ($P = 0.001$), with the patients who obtained cut-off score of more than four, related to upper gastrointestinal and breast cancers.

### Distress and problem list items

Evaluation of the detailed frequency of distress problems in the past week is presented in Table 3. Chi-square analyses were conducted to explore the relation of DT cut-off score to included items on the problem list (Table 4). With regard to practical problems, most of the patients had problem with transportation and then child care problems. While DT cut-off score was already related significantly to child care problems, one item (20%) ($P < 0.001$). With regard to family problems, most of the patients with DT score more than four experienced high distress of deal-

**Table 1** Demographic and clinical characteristics of study sample

| Variable | No. of patients | % |
|---|---|---|
| Age (years, mean ± SD) | 53.98 ± 15.55 | |
| Cancer diagnosis (months, mean ± SD) | 6.79 ± 5.98 | |
| Gender | | |
| Male | 159 | 62.1 |
| Female | 97 | 37.9 |
| Smoking | | |
| Yes | 51 | 19.9 |
| No | 205 | 80.1 |
| Addiction | | |
| Yes | 22 | 8.6 |
| No | 234 | 91.4 |
| Marital status | | |
| Single | 17 | 6.6 |
| Married | 203 | 79.3 |
| Divorced | 3 | 1.2 |
| Widowed | 33 | 12.9 |
| Location | | |
| Center | 144 | 56.2 |
| East | 62 | 24.2 |
| West | 39 | 15.2 |
| Out | 11 | 4.3 |
| Education in Gilan | | |
| Semi-illiterate | 88 | 34.4 |
| Elementary | 96 | 37.5 |
| High school | 56 | 21.9 |
| Graduate | 16 | 6.2 |
| Household income (R) | | |
| < 400,000 | 29 | 11.3 |
| 400,000–1,500,000 | 73 | 28.5 |
| < 1,500,000 | 154 | 60.2 |
| Treatment in the last month | | |
| Yes | 241 | 94.1 |
| No | 15 | 5.9 |
| Treatment type in last month | | |
| Radiotherapy | 175 | 72.6 |
| Surgery | 1 | 0.4 |
| Chemotherapy | 9 | 3.7 |
| Radiotherapy-surgery | 7 | 2.9 |
| Radiotherapy-chemotherapy | 47 | 19.5 |
| Radiotherapy-chemotherapy-surgery | 1 | 0.4 |
| Chemotherapy & Surgery | 1 | 0.4 |
| Carcinoma diagnosis | | |
| Upper gastrointestinal | 40 | 15.6 |
| Breast | 82 | 32 |
| Skin | 10 | 3.9 |
| Lymphoma | 21 | 8.2 |
| Gynecological | 13 | 5.1 |
| Colorectal | 28 | 10.9 |
| Prostate | 4 | 1.6 |
| Lung | 9 | 3.5 |
| Larynx | 19 | 7.4 |
| Bladder | 15 | 5.9 |
| Sarcoma | 10 | 3.9 |
| Unknown-metastasis | 5 | 2 |

R: Rial, the commonest currency in Iran

**Table 2** Frequency distribution of distress thermometer

| Score | No. of patients | % |
|---|---|---|
| 0 | 17 | 6.7 |
| 1 | 18 | 7.0 |
| 2 | 30 | 11.7 |
| 3 | 39 | 15.2 |
| 4 | 42 | 16.4 |
| 5 | 38 | 14.8 |
| 6 | 29 | 11.3 |
| 7 | 25 | 9.8 |
| 8 | 10 | 3.9 |
| 9 | 5 | 2.0 |
| 10 | 3 | 1.2 |

ing with children, also the score above the cut-off were more likely to these problems then about their parents (Table 5). About family problems, DT score was related significantly to two (100%) listed problems ($P < 0.001$). With regard to emotional problems, DT cutoff score was related significantly ($P < 0.001$) to 3 of 4 problems (75%). Patients who scored above the cutoff were more likely to report problems with depression, nervousness, fear and worry-sadness respectively. DT cut-off score didn't relate to spiritual problem ($P = 0.48$). With regard to physical problem, most of the patients complained about fatigue and then eating, changes in urination, constipation, appearance, feeling swollen, diarrhea and bathing-dressing problems, respectively. DT cutoff score was related significantly to 6 out of 8 listed problems (75%). Patients who scored above the cutoff score were more likely to report problems with fatigue and eating. With regard to physiological problems, the DT cutoff score was related significantly ($P < 0.001$) to 5 out of 6 problems (83.3%). While the patients who scored above the cutoff score were more likely to report problems with nausea then ingestion and getting around. About the other problem, the most common problems were sleep and pain problems, significantly related to higher cutoff points score.

## Discussion

Screening of distress in ambulatory patients with cancer showed that total number of reported concerns was associated with elevated level of distress. In this study, elevated distress scores of this sample correlated with patients-reported emotional sources of distress including: familial problems and to a lower degree, physiological source of distress. Moreover, patients with DT scores more than four were more likely to report at least or up to 22 of 32 items from the problem list. The observed association between DT scores more than four and significantly presented difference relation (6 from 8 for physical problem and 5 from 6 for physiological problem), would

**Table 3** Relation of thermometer cut-off score of 4 to categorical demographic and clinical variables

| Variable | DT Score > 4 | | DT Score < 4 | | Chi-Square | *P*-value |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | | |
| Gender | | | | | 0.024 | 0.89 |
| Male | 57 | 58.8 | 40 | 41.2 | | |
| Female | 95 | 59.7 | 64 | 40.3 | | |
| Smoking | | | | | 0.05 | 0.87 |
| Yes | 31 | 60.8 | 20 | 39.2 | | |
| No | 121 | 59 | 84 | 41 | | |
| Addiction | | | | | 0.18 | 0.82 |
| Yes | 14 | 63.6 | 8 | 36.4 | | |
| No | 138 | 59 | 96 | 41 | | |
| Marital status | | | | | 13.66 | 0.003 |
| Single | 5 | 29.4 | 12 | 70.6 | | |
| Married | 118 | 58.1 | 85 | 41.9 | | |
| Divorced | 3 | 100 | 0 | 0 | | |
| Widowed | 26 | 78.8 | 7 | 21.2 | | |
| Location | | | | | 4.18 | 0.24 |
| Center | 88 | 61.6 | 56 | 38.9 | | |
| East | 32 | 51.6 | 30 | 48.4 | | |
| West | 27 | 69.2 | 12 | 30.8 | | |
| out | 5 | 45.5 | 6 | 54.5 | | |
| Education in Gilan | | | | | 4.28 | 0.35 |
| Semi-illiterate | 67 | 76.1 | 21 | 23.9 | | |
| Elementary | 55 | 57.3 | 41 | 42.7 | | |
| High school | 28 | 50 | 28 | 50 | | |
| Graduate | 2 | 12.5 | 14 | 87.5 | | |
| Household income (R) | | | | | 4.53 | 0.10 |
| < 400,000 | 22 | 75.9 | 7 | 24.1 | | |
| 400,000–1,500,000 | 45 | 61.6 | 28 | 38.4 | | |
| < 1,500,000 | 85 | 55.2 | 69 | 44.8 | | |
| Treatment in the last month | | | | | 0.24 | 0.78 |
| Yes | 144 | 59.8 | 97 | 40.2 | | |
| No | 8 | 53.3 | 7 | 46.7 | | |
| Carcinoma diagnosis | | | | | 33.41 | 0.001 |
| Upper gastrointestinal | 34 | 85 | 6 | 15 | | |
| Breast | 32 | 39 | 50 | 61 | | |
| Skin | 6 | 60 | 4 | 40 | | |
| Lymphoma | 10 | 47.6 | 11 | 52.4 | | |
| Gynecological | 9 | 69.2 | 4 | 30.8 | | |
| Colorectal | 21 | 75 | 7 | 25 | | |
| Prostate | 2 | 50 | 2 | 50 | | |
| Lung | 7 | 77.8 | 2 | 22.2 | | |
| Larynx | 11 | 57.9 | 8 | 42.1 | | |
| Bladder | 11 | 73.3 | 4 | 26.7 | | |
| Sarcoma | 5 | 50 | 5 | 50 | | |
| Unknown-Metastasis | 4 | 80 | 1 | 20 | | |

R: Rial, the commonest currency in Iran

be present inconsistent with distressing nature evidence of cancer symptoms (fatigue, nausea, ingestion and getting around) [13]. Therefore, the similar expected results were promised in previous administrated studies on cancers [12, 14]. Our result the same as previous studies [12] suggested that spiritual and practical problems are less likely to be accompanied by clinically significant physiological distress. In the present, study each problem rated in terms of how much distress make from zero (no distress) to 10 (extreme distress), then splitting of the participants according to cutoff point of four were conducted. Our results showed that 59.4% of our studied individuals experienced significant distress more than four. However, this amount in previous studies was reported different (50% [15], 21.9% [16] and 34% [17]. It is probable that it was due to different analysis and cultural context. We didn't found any correlation between DT cut-off score of and gender. While previous studies using this DT measurement tool

**Table 4** Evaluation frequency detailed frequency of distress problems list in the past week

| Problems | Have | | Don't have | |
|---|---|---|---|---|
| | *n* | % | *n* | % |
| Practical Problems | | | | |
| Child Care | 78 | 30.5 | 178 | 60.5 |
| Housing | 11 | 4.3 | 245 | 95.7 |
| Insurance | 39 | 15.2 | 217 | 84.7 |
| Transportation | 132 | 52.0 | 123 | 48.0 |
| Work/School | 39 | 15.2 | 217 | 84.8 |
| Family Problems | | | | |
| Dealing with children | 55 | 21.5 | 201 | 78.5 |
| Dealing with partner | 47 | 18.4 | 209 | 81.6 |
| Emotional problems | | | | |
| Depression | 132 | 51.6 | 124 | 48.4 |
| Fears | 98 | 38.3 | 158 | 61.7 |
| Nervousness | 112 | 43.8 | 144 | 56.2 |
| Sadness-Worry | 10 | 3.9 | 246 | 96.1 |
| Spiritual/Religious | | | | |
| Relating to God | 11 | 4.3 | 245 | 95.7 |
| Physical Problems | | | | |
| Appearance | 40 | 15.6 | 216 | 84.8 |
| Bathing/Dressing | 12 | 4.7 | 244 | 95.3 |
| Changes in Urination | 48 | 18.8 | 208 | 81.2 |
| Constipation | 44 | 17.2 | 212 | 82.8 |
| Diarrhea | 19 | 7.4 | 237 | 92.6 |
| Eating | 87 | 34.0 | 169 | 66.0 |
| Fatigue | 127 | 49.6 | 129 | 50.4 |
| Feeling swollen | 31 | 12.1 | 225 | 87.9 |
| Physiological Problems | | | | |
| Fever | 16 | 6.2 | 240 | 93.8 |
| Getting around | 82 | 32.0 | 174 | 68.0 |
| Ingestion | 99 | 38.7 | 157 | 61.3 |
| Concentration | 31 | 12.1 | 225 | 87.9 |
| Mouth Sores | 26 | 10.2 | 230 | 98.8 |
| Nausea | 102 | 39.8 | 154 | 60.2 |
| Other Problems | | | | |
| Nose dry/Congested | 33 | 12.9 | 223 | 87.1 |
| Pain | 78 | 30.5 | 178 | 69.5 |
| Sexual | 61 | 23.8 | 195 | 76.2 |
| Skin dry/Itchy | 86 | 33.6 | 170 | 66.4 |
| Sleep | 134 | 52.3 | 122 | 47.7 |
| Tingling in hands/Feet | 58 | 27.7 | 198 | 77.3 |

**Table 5** Relation of thermometer cut-off score of 4 to frequency detailed frequency of distress problems in the past week

| Problems | DT Score > 4 (Have) | | DT Score < 4 (Don't have) | | *P*-value |
|---|---|---|---|---|---|
| | *n* | % | *n* | % | |
| Practical problems | | | | | |
| Child Care | 60 | 76.9 | 18 | 23.1 | 0.001 |
| Housing | 8 | 72.7 | 3 | 27.3 | 0.533 |
| Insurance | 28 | 71.8 | 11 | 28.2 | 0.11 |
| Transportation | 81 | 60.9 | 52 | 39.1 | 0.61 |
| Work/school | 21 | 53.8 | 18 | 46.2 | 0.48 |
| Family problems | | | | | |
| Dealing with children | 48 | 87.3 | 7 | 12.7 | 0.001 |
| Dealing with partner | 40 | 85.1 | 7 | 14.9 | 0.001 |
| Emotional problems | | | | | |
| Depression | 101 | 76.5 | 31 | 23.5 | 0.001 |
| Fears | 79 | 80.6 | 19 | 19.4 | 0.001 |
| Nervousness | 88 | 78.6 | 24 | 21.4 | 0.001 |
| Sadness-Worry | 9 | 90.0 | 1 | 10.0 | 0.48 |
| Spiritual/Religious | | | | | |
| Relating to God | 6 | 54.5 | 5 | 45.5 | 0.48 |
| Physical problems | | | | | |
| Appearance | 35 | 87.5 | 5 | 12.5 | 0.001 |
| Bathing/Dressing | 12 | 100.0 | 0 | 0 | 0.002 |
| Changes in urination | 36 | 75.0 | 12 | 25.0 | 0.015 |
| Constipation | 30 | 68.2 | 14 | 31.8 | 0.23 |
| Diarrhea | 16 | 84.2 | 3 | 15.8 | 0.02 |
| Eating | 69 | 79.3 | 18 | 20.7 | 0.001 |
| Fatigue | 97 | 76.4 | 30 | 23.6 | 0.001 |
| Feeling Swollen | 18 | 58.1 | 13 | 41.9 | 0.87 |
| Physiological problems | | | | | |
| Fever | 14 | 87.5 | 2 | 12.5 | 0.01 |
| Getting around | 70 | 85.4 | 12 | 14.6 | 0.001 |
| Ingestion | 81 | 81.8 | 18 | 18.2 | 0.001 |
| Concentration | 24 | 77.4 | 7 | 22.6 | 0.032 |
| Mouth sores | 18 | 69.4 | 8 | 30.8 | 0.30 |
| Nausea | 79 | 77.5 | 23 | 22.5 | 0.001 |
| Other problems | | | | | |
| Nose dry/Congested | 27 | 81.8 | 6 | 18.2 | 0.004 |
| Pain | 59 | 75.6 | 19 | 24.4 | 0.001 |
| Sexual | 35 | 57.4 | 26 | 42.6 | 0.766 |
| Skin dry/Itchy | 64 | 74.4 | 22 | 25.6 | 0.001 |
| Sleep | 95 | 70.9 | 39 | 29.1 | 0.001 |
| Tingling in hands/Feet | 45 | 77.6 | 13 | 22.4 | 0.001 |

[12] and other measures of distress, reported which female cases experienced higher level of psychological distress [14]. Like Strong *et al* [16], there was significant relation between age and emotional distress (DT score more than 4), as significant distress (87.5%) was attributed to older ages (≥ 75 years). In contrast of previous studies [17, 19], the significant relation was found between different cancer types and distress status. About the other demographic variables, according to our expectation and previous studies [12, 19, 20], more distress was related to married and then to single and divorced patients respectively. Besides, there wasn't relation between opium consumption or smoking and distress statues like previous studies [17, 20, 21]. However it is probable that the participants tried to conceal their addiction due to damaging social profile of smoking and addiction among them. Like Zeltzer *et al* [20] and Jacobsen *et al* [12] studies, we found lower experienced distress statues (DT < 4) in educated patients' comparing to non-educated ones, although some studies were demonstrated the inverse findings [19, 20]. In addition according to statistical analysis, there wasn't relation between household income, kind of treatment in the past and their living places with distress. Besides in similar studies [12, 19, 20], there was

no relation to distress and household income. However in present study, dividing income to categories are so tactful manner due to not precise accessibility to population incomes and concealment of their patients exact income for some legally sensitivity in Iranian population. According to our findings, it is probable that using expert physiological team and trained personnel might be able to reduce emotional distress problems and help the cancerous patients to struggle more positively against malignancy.

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# Postoperative intussusception in pediatric abdominal malignancies: early diagnosis and management

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**Abstract** ***Objective:*** The aim of this study was to review the incidence of postoperative intussusception (POI) in our patients with pediatric abdominal malignancies and the end result of management of these cases. ***Methods:*** From November 2007 till the end of December 2011, a total of 538 patients with different abdominal malignancies were operated upon by laparotomies in our hospital. Reoperations were required in 12 patients for post operative intestinal obstruction developed in the 1st postoperative month. Review of the identified cases focused on patient's characteristics, the primary tumor type, the primary surgical procedure, clinical and imaging features of the intussusceptions, timing and findings at the 2nd laparotomy and the end result of subsequent interventions. ***Results:*** Early post operative intestinal obstruction (within 1 month) developed in 12 patients of whom 8 patients had POI. Five patients had adhesive intestinal obstruction (one patient developed POI then adhesive obstruction). The median duration between the primary surgery and the onset of intestinal obstruction symptoms was 5 days (range 4–12 days) in the POI group and 24 days (range 10–30 days) in the adhesion group. Abdominal CT was done in all cases and it could properly diagnose POI and detect its site in the POI group while in the adhesion group it showed evidence of complete obstruction. Plain radiograph failed to detect signs of intestinal obstruction in 3 cases (two in the POI group and one in the adhesion group). In POI group simple reduction was done in 7 cases while resection anastmosis was done in 1 case due to gangrene of the ileocecal region. Adhesiolysis was done in the 5 cases of intestinal adhesion group. ***Conclusion:*** Early POI in pediatric abdominal cancer is a rare complication; however it should be kept in mind with high index of suspicion. Early diagnosis and intervention is essential for successful management. Abdominal CT is very helpful as it can detect the level and possible cause of obstruction.

**Key words** intussusception; postoperative intestinal obstruction

Early post operative intestinal obstruction (POI) in children is one of the challenging postoperative surgical complications. Detection of intestinal obstruction especially during early postoperative phase can be difficult and may be delayed because symptoms may mimic common postoperative complaints. Also in pediatric cancer patients, the side effects of chemotherapy and symptoms related to primary malignancy may obscure the diagnosis [1]. Although most cases of early post operative intestinal obstruction are due to intussusception, adhesive bands can also present with early post operative intestinal obstruction. The reported incidence of postoperative intussusception (POI) in children ranges from 0.29% to 16% [2–7]. In an early report by Cohen and colleagues in 1982 the incidence of POI in patients with neuroblastoma was 14.2% and they suggested that children with abdominal malignancy may be at increased risk [6]. The aim of this study was to review the incidence of POI in our group of patients with pediatric abdominal malignancies and the end result of management of these cases.

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## Patients and methods

Starting from November 2007 till the end of December 2011, a total of 538 patients were subjected to laparotomies for resection of different abdominal malignancies in the Children's Cancer Hospital, Egypt (CCH-E). Plain abdominal radiograph in both erect and supine views were performed for suspected cases of postoperative intestinal obstruction then abdominal CT scan post intravenous contrast was done to confirm the findings of plain radiograph and to identify the cause and localize the site of intestinal obstruction. The CT scans were interpreted and results were correlated with the post-laparotomy findings. Reoperations were required in 12 patients for

**Table 1** The incidence of early postoperative intestinal obstruction (IO) and postoperative intussusception (POI) in the different pathological groups

| Diagnosis | *n* | IO | | POI | |
|---|---|---|---|---|---|
| | | *n* | % | *n* | % |
| Wilms tumor | 232 | 6 | 2.6 | 4 | 1.7 |
| Neuroblastoma | 197 | 3 | 1.5 | 3 | 1.5 |
| Exrtragonadal GCTs | 24 | 1 | 4.1 | – | – |
| Hepatoblastoma | 21 | 2 | 9.5 | 1 | 4.7 |
| Ovarian tumors | 21 | – | – | – | – |
| Intestinal lymphoma | 19 | – | – | – | – |
| Soft tissue sarcomas | 17 | – | – | – | – |
| Others | 7 | – | – | – | – |
| Total | 538 | 12 | 2.2% | 8 | 1.5% |

post operative intestinal obstruction developing in the 1st postoperative month. Eight cases proved to have POI while the remaining 4 cases had adhesive bands. Review of the identified cases focused on patient's characteristics, the primary tumor type, the primary surgical procedure, clinical and imaging features of the intussusceptions, timing and findings at the 2nd procedure and the fate of subsequent interventions.

## Results

The study included 538 pediatric patients with different abdominal malignancies. Wilms tumor and Neuroblastoma were the commonest type of malignancy representing 79.7% of all cases. Early post operative intestinal obstruction (within 1 month) developed in 12 patients (2.2%) of whom POI developed in only 8 patients (1.5%). One patient developed POI that was corrected by surgical simple reduction, and then he was re-explored after 28 days for adhesive intestinal obstruction. The different pathological types and the incidence of POI in each type are illustrated in (Table 1). The group of POI consisted of 7 boys and 1 girl with a median age of 40.5 months (range 5–80 months). Seven cases of the POI group received neoadjuvant chemotherapy. The different ages and the number of cycles of chemotherapy are illustrated in (Table 2). The initial performed abdominal operations and the different presentations of post operative intestinal obstruction are illustrated in (Table 3). The median duration between the primary surgery and the onset of intestinal obstruction presentation was 5 days (range 4–12 days) in the POI group and 24 days (range 10–30 days) in the adhesion group. The imaging techniques and their findings are illustrated in (Table 4). In the 8 cases of POI, erect abdominal radiograph was done in only 5 cases, it showed multiple air fluid levels in 3 cases and it failed to detect signs of intestinal obstruction in two cases. Abdominal CT was done in all cases of POI group and could properly diagnose the presence of intussusception and its site in all of them. Of the adhesion group (5 cases), erect abdominal radiograph was done in 4 cases and it showed multiple air fluid levels in 3 cases, and failed to detect intestinal obstruction in one case. Abdominal CT was done in the 5 cases and it showed evidence of complete obstruction with proximal bowel dilatation and collapsed distal intestinal loops in all of them. The exploration findings of the POI and the intestinal adhesion groups are presented in (Table 4). In the POI group, 5 cases were ileo-ileal intussusceptions, one case was ileo-colic intussusception and 2 cases were ileo-ileo-cecal intussusceptions. Simple reduction was done in 7 cases while resection anastmosis was done in only 1 case due to gangrene of the ileocecal region with impending perforation (Table 4). Adhesiolysis was done in the 5 cases of intestinal adhesion group. All cases were successfully treated with no complications except one case with hepatoblastoma that had undergone right formal hepatectomy then right hemicolectomy for

**Table 2** Clinical characteristics of the early postoperative intestinal obstruction cases in our study

| Case No. | Diagnosis | Sex/Age | Preoperative chemotherapy | Preoperative radiotherapy |
|---|---|---|---|---|
| 1 | Left adrenal NB mass nodal complex | F/31 months | +/6 cycles | No |
| 2 | Hepatoblastoma of right lobe | M/7 months | +/6 cycles | No |
| 3 | Retroperitoneal GCT | F/22 months | no | No |
| 4 | Left Wilms | M/36 months | no | No |
| 5 | Left adrenal NB mass nodal complex | M/21 months | +/6 cycles | No |
| 5* | Left adrenal NB mass nodal complex | M/21 months | +/6 cycles | No |
| 6 | Left Wilms | M/80 months | no | No |
| 7 | Hepatoblastoma of left lobe | M/14 months | +/3 cycles | No |
| 8 | Left adrenal NB mass nodal complex | M/58 months | +/4 cycles | No |
| 9 | Left Wilms | M/5 months | +/6 weeks | No |
| 10 | Right Wilms | M/50 months | +/6 weeks | No |
| 11 | Bilateral Wilms | M/39 months | +/6 weeks | No |
| 12 | Left Wilms | M/61 months | +/6 weeks | No |

5*, same patient of No. 5. F, female; M, male.

**Table 3** Symptoms of early postoperative intestinal obstruction in our study

| No. | 1ry procedure | Date of 1ry procedure | Onset of IO symptoms (POD) | Symptoms of IO in chronological manner |
|---|---|---|---|---|
| 1 | Lt adrenalectomy and LNs debulking | 6/11/2008 | 11 | V, D |
| 2 | Rt hepatectomy | 14/1/2009 | 4 | D, V |
| 3 | Total resection of retroperitoneal GCT | 18/5/2009 | 30 | V, D,↑NGT output |
| 4 | Lt radical nephrectomy | 6/8/2009 | 10 | V, D |
| 5 | Biopsy from the adrenal NB mass nodal complex | 17/8/2009 | 4 | V, D |
| 5* | Same case of No 5 who developed POI and underwent simple Intussusception reduction after 7 days | 24/8/2009 | 29 | V, D, ↑NGT output |
| 6 | Lt radical nephrectomy | 28/10/2009 | 6 | V, D |
| 7 | Lt hepatectomy | 1/3/2010 | 20 | V, D, ↑NGT output |
| 8 | Lt adrenalectomy and LNs debulking | 17/3/2010 | 4 | V, D |
| 9 | Lt radical nephrectomy | 29/12/2010 | 12 | P, V, D |
| 10 | Rt radical nephrectomy | 28/3/2011 | 4 | V, D |
| 11 | Left radical nephrectomy + right partial nephrectomy | 10/11/2011 | 24 | V, D |
| 12 | Left radical nephrectomy + right hepatectomy for large liver deposits | 21/12/2011 | 9 | P, V |

V: vomiting; D: abdominal distension; NGT: naso-gastric tube; P: abdominal pain; POD: postoperative day

**Table 4** Radiological findings, surgical management, and end results of early postoperative intestinal obstruction cases in our study

| No. | Abdominal X ray | | Abdominal CT | |
|---|---|---|---|---|
| | Timing POD | Findings | Timing POD | Findings |
| 1 | 13 | Multiple Small intestinal air-fluid levels | 13 | Ileo-ileal intussusception |
| 2 | Not done | – | 7 | Ileo-colic intussusception |
| 3 | 32 | Multiple Small intestinal air-fluid levels | 33 | Dilated proximal and collapsed distal small intestine |
| 4 | 12 | Multiple Small intestinal air-fluid levels | 12 | Dilated proximal and collapsed distal small intestine |
| 5 | 4 | Multiple Small intestinal air-fluid levels | 6 | Ileo-ileal intussusception |
| 5* | 32 | Multiple Small intestinal air-fluid levels | 33 | Dilated proximal and collapsed distal small intestine |
| 6 | 7 | No evidence of intestinal obstruction | 7 | Ileo-ileal intussusception |
| 7 | 22 | No evidence of intestinal obstruction | 23 | Dilated proximal and collapsed distal small intestine |
| 8 | Not done | – | 4 | Ileo-colic intussusception |
| 9 | Not done | – | 18 | Ileo-colic intussusception |
| 10 | 5 | Multiple Small intestinal air-fluid levels | 5 | Ileo-ileal intussusception |
| 11 | Not done | – | 27 | Dilated proximal and collapsed distal small intestine |
| 12 | 10 | No evidence of intestinall obstruction | 11 | Ileo-ileal intussusception |

| No. | 2ry procedure | | | End result |
|---|---|---|---|---|
| | Timing POD | Findings | Procedure | |
| 1 | 13 | Ileo-ileal intussusception | Simple reduction | Uneventful |
| 2 | 8 | Ileo-colic intussusception with gangrene of ileocecal region and impending perforation | Rt hemicolectomy | Died 12 days after 2ry procedure |
| 3 | 34 | Adhesion at operative bed | Adhesiolysis | Uneventful |
| 4 | 12 | Adhesions between terminal ilum and pelvic wall | Adhesiolysis | Uneventful |
| 5 | 7 | Ileo-ileal intussusception | Simple reduction | Developed 2nd IO |
| 5* | 35 | Adhesive band | Adhesiolysis | Uneventful |
| 6 | 8 | Ileo-ileal intussusception | Simple reduction | Uneventful |
| 7 | 24 | Adhesive band | Adhesolysis | Uneventful |
| 8 | 5 days | Ileo-ileo-cecal intussusception | Simple reduction | Uneventful |
| 10 | 19 | Ileo-ileo-cecal intussusception | Simple reduction | Uneventful |
| 10 | 5 | Ileo-ileal intussusception | Simple reduction | Uneventful |
| 11 | 28 | Multiple adhesive bands | Adhesiolysis | Uneventful |
| 12 | 12 | Ileo-ileal intussusception | Simple reduction | Uneventful |

postoperative ileo-colic intussusception. The patient developed postoperative pneumonia and died 12 days following the 2ry procedure due to multiple-organ failure. Fig. 1–4 show the comparison of abdominal CT, erect ab-

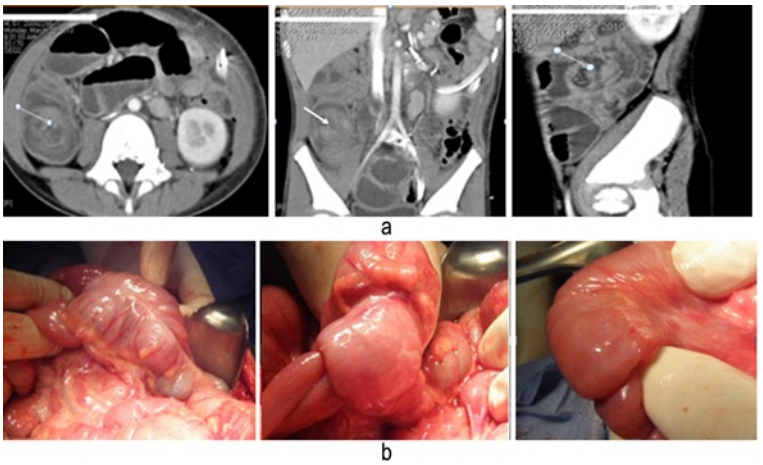


**Fig. 1** (a) Abdominal CT scan of case No. 8 shows small bowel dilatation with intussusception can be properly diagnosed at ileocecal region showing target sign (arrows); (b) Operative view of the same patient showing ileo-ileo-cecal intussusception on the left, reduction of the ileo-cecal intussusception in the middle and reduction of the ileo-ileal intussusception on the right

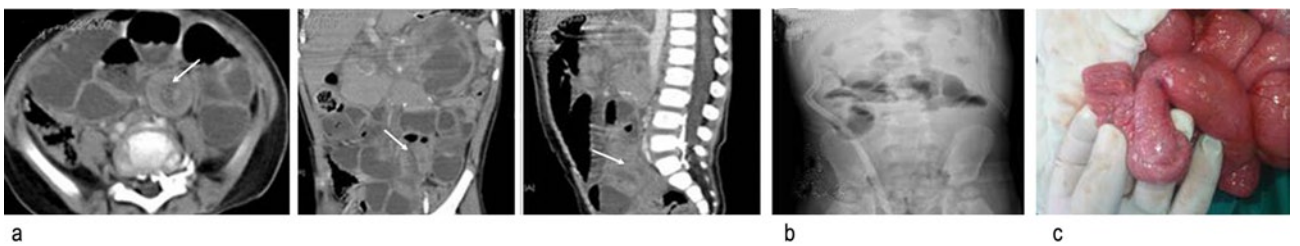


**Fig. 2** (a) Abdominal CT scan of case No. 5 with ileo-ileal intussusception showing the target sign (arrows); (b) Erect abdominal radiograph of the same patient showing multiple small intestinal air-fluid levels; (c) Operative view of the same patient showing the ileo-ileal intussusception

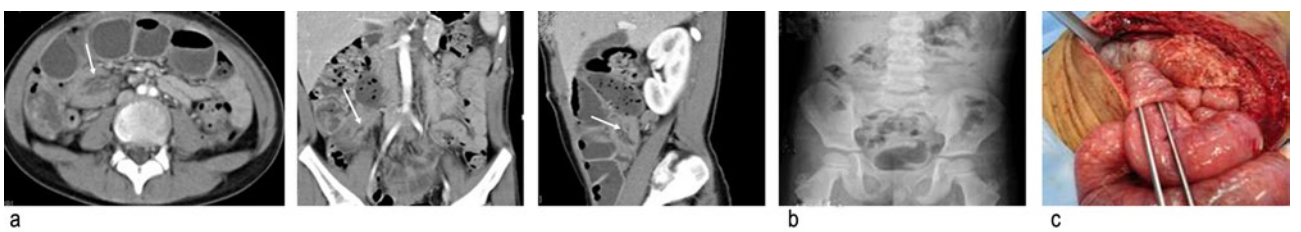


**Fig. 3** (a) Abdominal CT scan of of case No 6 with ileo-ileal intussusception (arrows); (b) Erect abdominal radiograph of the same patient showing no evidence of intestinal obstruction; (c) Operative view of the same patient showing the ileo-ileal intussusception

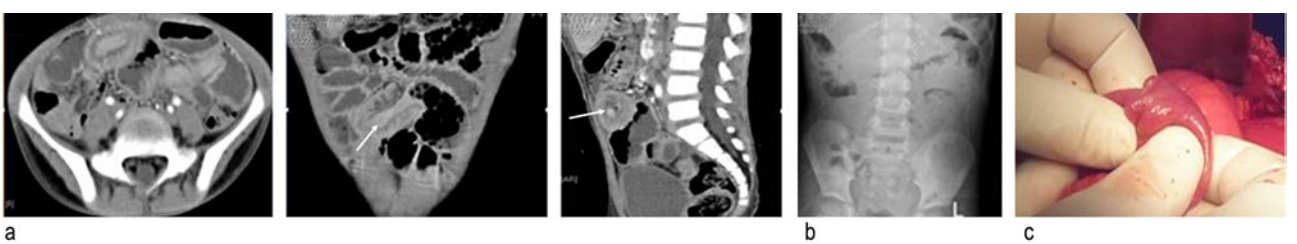


**Fig. 4** (a) Abdominal CT scan of of case No 12 with ileo-ileal intussusception showing the target sign in the axial and sagittal views and the double loop configuration in the coronal view with dilated proximal loops (arrows); (b) Erect abdominal radiograph of the same patient showing no evidence of intestinal obstruction; (c) Operative view of the same patient showing reduction of the ileo-ileal intussusception

dominal radiograph and operative view in different cases in our study.

## Discussion

Postoperative bowel obstruction is a major complication of abdominal surgery. In our study which included 538 patients with pediatric abdominal cancer, the inci-

dence of postoperative intussusception (POI) was 1.5% (8/538) which is higher than other series in general pediatric hospitals which reported a low incidence of POI (0.29%) [2], but lower than other series of pediatric cancer hospitals (2.2% to 16%) [4–7]. This variation can be explained by the type of primary surgery and whether preoperative chemotherapy was given or not. Some operations had higher incidence of POI where retroperitoneal dissection is done (e.g. neuroblastoma and Wilms tumor) [4–6], Hirschsprung disease and gastroeosophageal reflux (GER) [2].

Various theories attributed POI to certain pathogenic factors to explain its etiology. There is evidence that the operative procedure leads to an edematous reaction with subsequent perfusion deficits and motility disturbances of the intestine [8, 9]. Many reports emphasize the relationship between intussusception and lengthy operations with extensive handling of the intestine and retroperitoneal dissection [2]. Manipulation of the small bowel during laparotomy can cause local damage, hypoxia, spasm and edema. This functionally altered segment may act as lead point for intussusception. Another trigger mechanism may be the neurotoxin effects of chemotherapy (vincristine) and radiation therapy [10]. In our study neoadjuvant chemotherapy was given in 7 cases out of the eight cases that developed POI but preoperative radiotherapy was not given in any case. The role played by neuroendocrine factors is still unknown [2].

Ninety percent of cases due to POI occur in the first 2 weeks, in contrast post operative obstruction due to adhesions develop weeks or more after operation in 75 percent of patients [8]. Similarly in our study which included cases with early intestinal obstruction within one month of surgery, the clinical presentation of POI group was earlier than the adhesion group. The median duration between the primary surgery and the onset of intestinal obstruction presentation was 5 days (range 4–12 days) in the POI group and 24 days (range 10–30 days) in the adhesion group.

The diagnosis of POI can be overlooked because the clinical presentation can be confused with the much more common presentation of ileus and the minimal symptoms [11]. Pain in these patients is usually alleviated by routine post operative pain medication, vomiting is less noticeable because nasogastric tube is typically present, mass is difficult to palpate in an already tender abdomen and bleeding per rectum rarely occurs [12]. Nasogastric tube is usually removed in our cases in the 1st post operative day unless there is intestinal anastomosis. Vomiting, abdominal distension, and abdominal pain were the most common presentations in our cases. We did encounter neither bleeding per rectum nor palpate abdominal mass in any case.

Postoperative intussusception presents diagnostic challenge to the radiologist. The obstruction usually involves bowel segment that are infrequently affected by typical primary intussusception. Plain abdominal radiograph may be helpful in demonstrating multiple air fluid levels of different heights [13]. Abdominal ultrasound can be a helpful tool to determine primary intussusception, yet in the early postoperative period with tender abdomen and gaseous distension it is usually problematic [1]. Abdominal CT is more helpful to diagnose the cause of obstruction as it demonstrates the collapsed, intussuscepted proximal bowel (intussusceptum) with the mesenteric fat and vessels lying within the wall of the distal bowel (intussuscepient). On cross-section images, the intussusception has a target-like appearance [13].

In our study Abdominal CT was done in all cases of early postoperative intestinal obstruction and it was able to detect the 8 cases of POI denoting also the site of intussusception. In the intestinal adhesion group abdominal CT was able to confirm the presence of mechanical obstruction and predict its site. Although abdominal erect radiograph was helpful to detect intestinal obstruction in 6 cases it did not conclude its cause and it failed to show radiologic evidence of obstruction in 3 cases (two in the POI group and one in the adhesion group).

## Conclusion

Early postoperative intussusception following surgery for pediatric abdominal cancer is an infrequent complication, however it should be kept in mind with high index of suspicion as early diagnosis may be difficult in the early postoperative course. Early diagnosis and intervention is essential for successful management with minimal complications and abdominal CT is very helpful as it does not only establish the diagnosis of intestinal obstruction but it can also detect the site and possible cause of obstruction. The early use of CT is crucial to avoid intestinal wall damage and necrosis resulting from overlooked intussusception.

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# Sonographic guidance for tunneled central venous catheters insertion in pediatric oncologic patients: guided punctures and guide wire localization

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**Abstract** ***Objective:*** Totally implantable devices (TIDs) and external tunneled catheters (ETCs) became a basic requirement in the treatment of pediatric oncologic patients. Techniques for implantation and confirmation of proper position vary among different centers. The article presented different techniques for sonographic guided puncture of the target central vein and confirmation of the proper position of tunneled catheters. ***Methods:*** This was an observational study with a single cross-over phase, in which operators initially used the open cut down technique and subsequently converted to the ultrasound guided technique. Internal jugular vein (IJV) was used in all cases. ***Results:*** In ultrasound guided group, TIDs were inserted in 121 cases while ETCs were inserted in 13 cases. Ultrasound was successful in guiding IJV puncture from the first trial in all cases and in guide-wire localization in the right atrium in 132 cases. There were no reported cases of hematoma, pneumothorax, hemothorax, catheter malposition or surgical-site infection (SSI) in the perioperative period. In the open cut down group, TIDs were inserted in 119 cases. Two patients developed post operative hematoma and one of them developed SSI. The mean time of ultrasound guided TIDs was (30.04 ± 1.1) minutes which was significantly lower than the mean time of cases done by the open cut down technique (45.4 ± 3.1) minutes ($P < 0.0001$). ***Conclusion:*** Ultrasound guidance is helpful for insertion of TIDs and ETCs in the IJV in pediatric oncologic patients. It minimizes the need for open cut downs and fluoroscopy.

**Key words** tunneled central venous catheters (tunneled CVCs); pediatric; ultrasound

Reliable central venous access is a crucial part in the treatment of haemato-oncology diseases. Typical central venous catheters (CVCs) for mid and long term therapy in oncology are either external tunneled catheters (ETCs) (e.g. Hickman) or totally implantable devices (TIDs) (port system) [1]. Catheters are placed by either open cut down on the target vein or by percutaneous puncture using anatomical landmarks to guide the site of puncture. Intraoperative ultrasound (U/S) localization of the target vein and fluoroscopic direction of the guide wire have been used to add to the safety and efficiency of the closed technique [2–9]. Fluoroscopy requires special radiography equipment, technician and in addition it exposes the operating staff to radiation. Other alternatives to flouroscopy include: intravascular electrocardiography, catheter sensing devices or transeosophageal echocardiography [10, 11].

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In our hospital (Children's Cancer Hospital, Cairo, Egypt) we developed a new way to localize the target vein and the guide wire in a rather simple way without the need for radiation exposure. This is done by localizing the guide wire by the same U/S kit that is already used for guiding venipuncture. The aim of this study was first to assess the technical feasibility and efficiency of different techniques of U/S guided puncture, secondly the use of U/S confirmation of the proper position of tunneled catheters used for pediatric oncologic patients.

## Patients and methods

This was an observational study with a single cross-over phase, in which operators initially used the open cut down technique between July 2009 and the end of June 2010 in 119 patients (control period) and subsequently converted to the ultrasound guided technique since July 2010. One hundred and thirty four patients were done

between July 2010 and the end of June 2011 using the new technique (study period). All procedures were done by the same operators (4 pediatric surgical oncology consultants). The change in the technique was made after they had received adequate ultrasound training in the Radiology Department in our hospital. Patients were referred to the Department of Surgery in Children's Cancer Hospital, Egypt (CCH-E) for implantation of tunneled central venous catheters. All data of the patients and operative procedures were entered and recollected through our computerized hospital information system. The study was approved by the hospital IRB. Informed consent was taken from the guardians of all patients included in the study. Exclusion criteria for implantation were: platelet count < 50 /mL$^3$, PC < 50%, INR > 1.5 and the presence of systemic infection. Internal jugular vein (IJV) was the target vein in all cases. History concerning previous central venous catheter placement and target vein thrombosis was obtained before planning the procedure. History of previous central venous catheter placement was not considered a contraindication so long that the target vein was patent as evident by U/S. All cases were done under general anesthesia in class 100 OR (operating rooms equipped with HEPA filters).

In the ultrasound guided group, U/S (BK medical, using 5 to 10 MHz LINEAR transducer) examination of the neck on both sides was performed thereby thrombosis of IJV was ruled out by compression sonography before starting the procedure. The patient was placed in supine Trendelenberg position with neck extension and rotation to the contra lateral side of surgery then U/S examination evaluates the relationship of the CCA and IJV as well as the diameter of the IJV to determine the optimum implantation site and size of the tunneled catheter. The preferred site was the Rt. IJV in the lower third of the neck. In case of small or thrombosed Rt. IJV the left IJV was used as the implantation site.

Three techniques were used to successfully puncture the IJV. In the first technique the U/S transducer was put perpendicular to the vein. When the vein was centered on the screen it would be deep to the middle of the probe. The puncture was to be made at this point (Fig. 1). In the 2nd technique the puncture was done at the periphery of the probe and the vein was approached laterally (Fig. 2). The 3rd technique was similar to the first technique but when the vein was localized in an axial view the probe was turned 90 degrees around its central point to get a longitudinal axis view of the vein. The needle then punctured the skin at the cephalic end of the probe and was directed under U/S visualization to the vein (Fig. 3). The chosen site in the skin for vein puncture was opened by scalpel to facilitate entry through the skin to avoid compression of the vein. Once the needle entered the venous lumen, the guide wire was introduced and pushed into the superior vena cava (SVC). Proper direction and position of the guide wire was determined by putting the U/S probe in the epigastrium directed cranially and to the right to show the Rt. atrium and terminal part of the SVC (Fig. 4). The correct intravenous position of the guide wire could be confirmed by observing the J of the guide wire in the Rt. atrium or the cavoatrial junction (Fig. 4). In case of TIDs a subcutaneous chest pocket was prepared for the port. The catheter was then connected to the port and tunneled to come out at a separate point lateral to the puncture point thus making a station lateral in the neck rather than making the tunnel directly from the pocket to the puncture site. This loop provided 2 benefits. First it avoided the acute kink of the catheter at the site of introduction in the vein and in addition it provided the benefit that you could modify the site of the catheter tip in a range of 1 cm by increasing or decreasing the arc of rotation of the catheter in the subcutaneous tissue of the neck to optimize its position. The catheter was cut based on the guide wire length (measured during localization of the J of the wire in the cavoatrial junction). This was followed by introduction of the catheter using the standard Seldinger technique. Routine intraoperative radiology using image intensifier was done at the end of the procedure to insure proper catheter tip site and to rule out complications like pneumothorax or heamothorax. Chest radiograph was done in all cases 4–6 h after surgery to rule out delayed pneumothorx. Perioperative complications including intraoperative complications and those occurring within one month of surgery were collected and analyzed. This group of patients (ultrasound guided group) was compared to the open cut down group regarding the length of the procedure and perioperative complications. Length of the procedure was defined as the time between the initial cutaneous sterilization and placement of the dressing.

## Results

We evaluated 253 procedures (119 in the open cut down phase and 134 in the ultrasound phase) for insertion of tunneled CVCs. The number of catheters placed corresponds to the number of patients enrolled. The clinical characteristics of our patients were presented in Table 1. In the ultrasound guided group, the mean ages were 4.8 & 6.7 years for the TIDs & ETCs groups respectively and the mean weights were 18.9 & 27.1 kg respectively. In the open cut down group, the mean age was 5.2 years and the mean weight was 19.4 kg.

In the ultrasound group TIDs were inserted in 121 cases and ETCs were inserted in 13 cases. Right IJV was used in 123 cases and the left IJV was used in 11 cases due to thrombosis of the right IJV in 3 cases and hematoma around the vein in 8 cases due to previous trial of

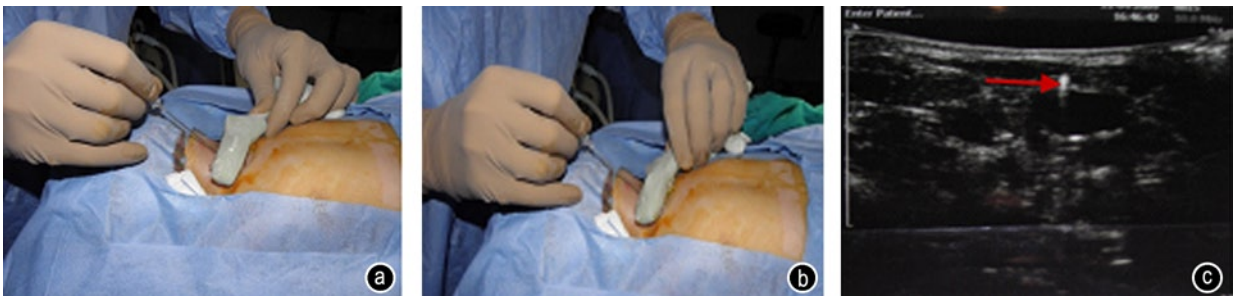

**Fig. 1** Anterior approach to the IJV. With the vein at the middle of the screen (c) it will be underneath the middle of the probe (a). Note that in the Fig. 1a the direction of the needle and the probe was at an acute angle to each other; this helped visualization of the needle as soon as it punctured the skin. On the contrary, Fig. 1b showed a less helpful configuration where the probe was directed towards the clavicle; this would require the needle to travel a long distance under the skin to reach the field of the ultrasound probe

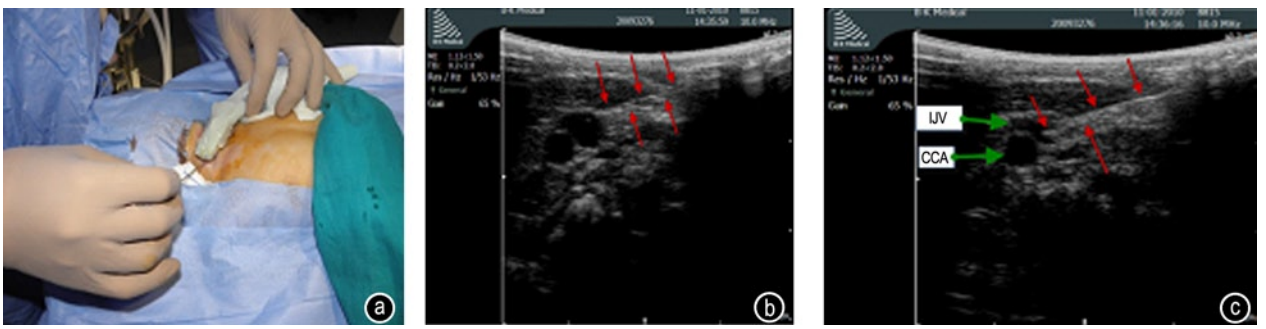


**Fig. 2** Lateral approach to the vein (the operator was at the head of the patient). From Left to right: the position of the probe and the needle (a), the needle was running in the soft tissue of the neck stopping at the IJV wall (b), and the needle was advanced so that the tip was intraluminal (c)

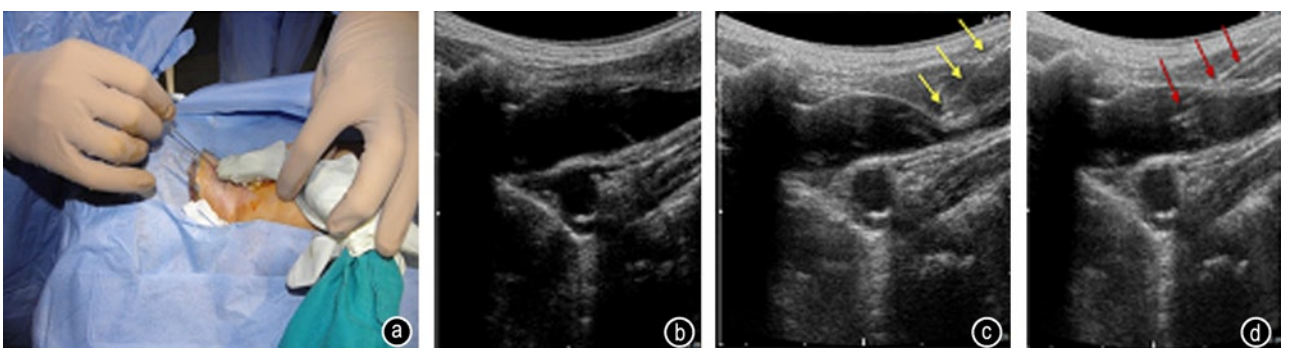

**Fig. 3** Anterior approach with longitudinal position of the probe. From left to right: the position of the probe and the needle (a), the IJV (b), the needle was advanced pocking the vein (c), and the needle was inside the IJV (d)

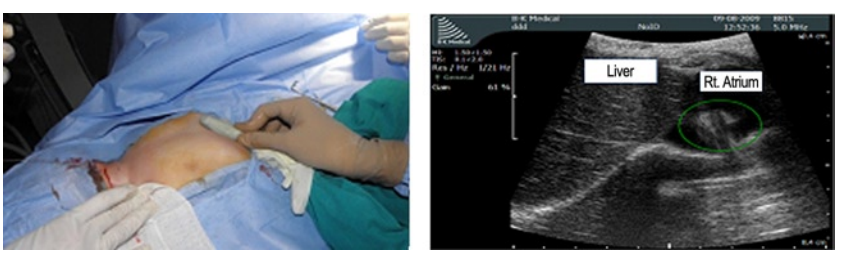


**Fig. 4** Confirmation of proper direction and position of the guide wire using the ultrasound. Left: demonstration of the position of the probe in the epigastrium. Right: the J of the guide wire was seen in the Rt. atrium

**Table 1** Clinical characteristics of our patients

| | Uitrasound guided TIDs (*n* = 121) | Ultrasound guided EIDs (*n* = 13) | Open cut down TIDs (*n* = 119) |
|---|---|---|---|
| Age (years) | | | |
| Mean | 4.8 | 6.7 | 5.2 |
| Median | 3.6 | 4.5 | 4.1 |
| Range | 0.16–17.5 | 2.3–13 | 0.25–16.5 |
| Body weight (kg) | | | |
| Mean | 18.9 | 27.1 | 19.4 |
| Median | 14.7 | 21.0 | 15.6 |
| Range | 4–59 | 10–48 | 5–62 |
| Sex (male : female; *n*) | 62:59 | 8:5 | 63:56 |
| Primary malignancy [*n* (%)] | | | |
| ALL | 60 (49.6%) | | 61 (51.3%) |
| AML | 48 (39.6%) | | 45 (37.8%) |
| NHL | | 8 (61.5%) | |
| Neuroblastoma | | 5 (38.5%) | |
| RMS | 2 (1.7%) | | 2 (1.7%) |
| Bone tumors | 2 (1.7%) | | 3 (2.5%) |
| Hepatoblastoma | 2 (1.7%) | | 2 (1.7%) |
| Others | 7 (5.7%) | | 6 (5.0%) |

TIDs: totally implantable devices; ETCs: external tunneled catheters; ALL: acute lymphoid leukemia; AML: acute myeloid leukemia; NHL: non-Hodgkin's lymphoma; RMS: rhabdomyosarcoma

central venous line insertion. Using the real-time sonographic guidance venous puncture from the first attempt was successful in all cases. Guide wire localization in the right atrium by U/S linear probe in the epigastrium was successful in all cases except two cases (one case had large left lobe hepatoblastoma and the other case was 16 years old obese boy with leg osteosarcoma).

Intraoperative radiology using image intensifier done at the end of the procedure showed that, in five cases the tip was found just in the upper atrium, in 36 cases it was at the junction between the SVC and the right atrium while in the remaining cases it was lying within 0.5 cm proximal to that junction. There was no need to change the tip site of the catheter in any case after the results of the C-arm. Chest radiography done after 4–6 h proved that no case developed late pneumothorax. Technical success was 100% and there were no reported cases of hematoma, pneumothorax, hemothorax, catheter malposition, surgical-site infection (SSI) or symptomatic deep venous thrombosis during the perioperative period.

In the open cut down group, TIDs were inserted in 119 patients and there were no cases of ETCs as we useed the latter only for intensified therapy during bone marrow transplantation (BMT). The unit of BMT started working in our hospital since October 2010. Right IJV was used in 107 cases and the left IJV was used in 12 cases due to thrombosis of the right IJV in 5 cases and hematoma around the vein in 7 cases due to previous trial of central venous line insertion. Two patients developed post operative hematoma and one of them developed SSI. In the latter case the catheter was removed and another one was reinserted later on after resolution of infection by proper antibiotics. There were no reported cases of pneumothorax, hemothorax, catheter malposition or symptomatic deep venous thrombosis during the perioperative period.

All cases were done under general anesthesia in class 100 OR (operating rooms equipped with HEPA filters) with no reported significant anesthetic complications. It needed little training to master the technique of sonar guided tunneled CVCs insertion by the operating surgeons. Being a simple procedure it didn't burden our scheduling in the operating rooms and was planned in the same day or the next day after being requested from the Pediatric Oncology Department.

The mean time of ultrasound guided TIDs insertion was (30.04 ± 1.1) minutes which was significantly lower than the mean time of cases done by the open cut down technique (45.4 ± 3.1) minutes ($P < 0.0001$). The mean time of ultrasound guided ETCs insertion was (19.8 ± 1.2) min.

## Discussion

Totally implantable devices (TIDs) are venous access systems that provide long-term and safe access to the vascular system for the delivery of antineoplastic medications [12]. In patients with leukemia multi-lumen, external tunneled catheters (ETCs) are the standard care, especially in the intensified therapy during bone marrow transplantation. They allow the application of chemotherapy, antibiotics, parenteral nutrition, blood products, mass transfusion, and blood withdrawal. The lumen of

port catheters is not large enough for complex therapy during bone marrow transplantation [2, 5].

Complications occurring during TIDs or ETCs implantation include inaccurate positioning of the catheter tip, pneumothorax, hematoma, twisting or kinking of the catheter, postoperative catheter fracture or rupture and infection [10, 13].

Some investigators have advocated that TIDs can be placed without the aid of catheter localizing devices or intraoperative imaging, reducing cost and surgical time [10, 14, 15]. Others advise the use of both real-time sonography and fluoroscopy to guide venipuncture and catheter insertion. This combined technique allows high rate of technical success and low rates of complications. It offers several advantages over blind placement particularly in children including avoidance of pneumothorax or hematoma resulting from arterial puncture and it also decreases the number of anatomical sites attempted [5, 7, 16, 17].

Sonographic guidance can be used for planning the procedure, performing venipuncture, and identifying alternative routes of access in patients with central venous obstruction. Before the procedure sonography can be used to localize appropriate-sized veins and identify occluded veins. During the procedure real-time sonography guidance enables to puncture the small IJVs of children successfully using a single puncture in most cases [3]. Previous studies showed that the duration of venous puncture and the number of attempted punctures increase the risk of thrombosis, possibly due to endothelial damage during the puncture [18]. In our study using the real-time sonographic guidance, venous puncture from the first attempt was successful in all cases and we did not report any case of post insertion symptomatic central venous thrombosis in the perioperative period.

We used three approaches to the IJV guided by the U/S. It was the operator preference to choose which ever to do, however sometimes the built of the patient and the shape of the probe could direct the operator to the choice. For in some patients the configuration of the neck and clavicle will make the position of the probe difficult for the 3rd technique. The 3rd technique might be the best in terms of visualization of the needle all through its course, but it requires more experience and training. The 1st technique with puncturing the vein at midpoint of the probe is the simplest to learn with the disadvantage of not enabling viewing the needle all through its course. In order to enable better viewing of the needle, the operator has to be conscious about the relation of the probe to the needle; they have to be in acute angle to each other, i.e. the needle directed caudal while the probe is either perpendicular to skin or inclined slightly cephalad but not directed towards the clavicle.

The presumed disadvantages of ultrasound are the additional costs of consumable and additional time necessary for the coverage of the ultrasound with its cover kit however the additional cost is negligible in relation to the overall costs and that additional time is compensated by the faster, ultrasound-guided venous puncture [5, 19]. In addition, ultrasound guidance could show cost effectiveness in recent meta-analysis [20, 21]. In our study, the mean time of ultrasound guided TIDs insertion was (30.04 ± 1.1) minutes which was significantly lower than the mean time of TIDs cases done by the open cut down technique (45.4 ± 3.1) minutes ($P < 0.0001$). The mean time of ultrasound guided ETCs insertion was (19.8 ± 1.2) minutes.

Fluoroscopic guidance for advancement of the guide wire and sheath virtually eliminates inadvertent central venous rupture [3]. In our study we did not use the fluoroscopic guidance but instead of that we depended on guide wire localization in the right atrium by U/S linear probe in the epigastrium before introduction of the trocar sheath. This was successful in all cases except two cases (one case had large left lobe hepatoblastoma and the other case was 16 years old obese boy with leg osteosarcoma). Another advantage of the image intensifier is to exclude intraoperative pneumbothorax and haemothorax however the incidence of pneumothrax and haemothorax is markedly decreased using U/S guided venipuncture. Another issue is that routine intraoperative or immediate postoperative chest radiography may not be able to detect pneumbothorax. Brown and colleagues [22] stated that the incidence of pneumothorax after fluoroscopic-guided subclavian central venous port placement (SCVP) was low yet it is not usually detected by intraoperative fluoroscopy or by routine postoperative chest X-ray. They concluded that the practice of routine postoperative chest radiography after SCVP placement is not necessary and should be replaced with diagnostic chest radiography only if symptoms develop. There were no reported cases of delayed pneumothorax in our study when postoperative chest X-ray was done after 4–6 h thus we do not recommend routine postoperative chest radiography after sonar guided IJV catheterization and this should be done only if symptoms develop. The incidence of venous thrombosis, catheter occlusion, and catheter migration is minimized by positioning the catheter tip as close to the cavoatrial junction as possible or at the upper right atrium, as insisted by most investigators [23–25]. Fluoroscopy has the advantage of accurately localizing the site of the catheter tip. Although catheter tip could be visualized in the distal part of the SVC using the ultrasound probe used for echocardiography in our hospital, this probe was not available in the OR. It has been difficult in our work to make such localization using the ultrasound superficial probe that has been used for IJV puncture and the guide wire localization. As an alternative, we used the marks on the guide wire to estimate the length needed from the catheter and cut it accordingly. This measurement is to be

taken when the J of the wire is seen in the right atrium as demonstrated earlier. There is no need to be obsessed about precisely locating the catheter tip in the cavoatrial junction. A bit proximal or distal is equally safe and effective so long that there are no arrhythmias. We routinely did intraoperative chest radiograph at the end of the procedure to confirm the site of the tip of the catheter and there was no need to change the tip site of the catheter in any case of our study based on the results of the C-arm.

The choice of CVCs size should be predicted, not only on the primary disease, but also on the child's age, weight, and height. Insertion of CVCs larger than 6F in children less than 1 year of age, less than 10 kg in weight, or less than 75 cm in height, was associated with higher complications compared with other settings [26]. It has to be noted that, using the commercially available percutaneous sets for central venous catheters, one should put in mind that the choice of proper kit-size is not only about the diameter of the catheter. It is as well a function of the diameter of the introducer sheath. Introducer sheaths and dilators are relatively rigid tools. If they are bigger than what would be adapted by the vein, tears can ensue. In our study ultrasound was helpful to choose the best size of the used catheter and thus we did not report any catheter related complications.

Subclavian vein access had been the recommended approach for placing CVCs. The anatomical landmark method for subclavian access remains a highly successful and nonequipment-dependent method for rapid central access. More recently, the IJV approach has emerged as the preferred route for long-term central venous access. However, variations in IJV anatomy make the landmark method less reliable. Use of two-dimensional real-time ultrasound during IJV access is associated with better access, a lower complication rate, and faster access [27]. The puncture of the subclavian vein have higher incidence of pneumothorax (0.6%–4.3%) in all published studies [28–35]. In our group of patients, we had no pneumothorax using the IJV in all cases. Our results correspond to the results of other studies [36, 37].

The main limitation of our study is that late complications are not included. In addition to the technique and site of catheter insertion other factors will affect the frequency of catheter related late complications including type of the primary tumor, type and frequency of chemotherapy administration, and catheter management. A well trained nursing staff team for management of tunneled CVCs was established in our hospital since March 2012 and since that time they took the responsibility of management of tunneled CVCs at any site of the hospital. Before that time there was no defined team for that purpose. An ongoing study is done now in our hospital to analyze the data of late complications of tunneled CVCs to detect the possible causes and whether the establishment of this nursing staff team has an impact on decreasing the frequency of these complications.

## Conclusion

Ultrasound guidance is helpful for insertion of TIDs and ETCs in the IJV in pediatric oncologic patients. It minimizes the need for open cut downs on the target veins yet avoids the complications of blind percutaneous punctures. In addition it minimizes the need for fluoroscopy avoiding the risk of excessive radiation to the patient and operators.

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# Diaphragmatic hernia complicated with intestinal obstruction with colon perforation after surgery for esophageal cancer: a case report

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**Abstract** We reported a case of diaphragmatic hernia complicated with intestinal obstruction with colon perforation after surgery for esophageal cancer. In this case, the conservative treatment took too long, which delayed the diagnosis and treatment and resulted in colon perforation. After computed tomography confirmed the diagnosis, an emergency operation was performed. During the operation, we found colon perforation. Because pollution of thoracic cavity was serious, we performed proximal end colon neostomy. The patient recovered and discharged with active treatment 35 days after operation. We consider surgical repair of the diaphragmatic hernia is recommended to avoid the potentially disastrous complications, such as strangulation or perforation of the herniated contents, which can threaten the life of the patient if diagnosis is delayed.

**Key words** diaphragmatic hernia; colon perforation; esophageal cancer

Esophagectomy through left posterolateral thoracotomy is a well known procedure to the traditional transthoracic approach for esophageal disease. Diaphragmatic hernia is a rare but preventable postoperative complication of this procedure. It can occur early or late after operation and the varying nature of the clinical presentation may cause delay in diagnosis. Surgical repair of the diaphragmatic hernia is recommended to avoid the potentially disastrous complications, such as strangulation or perforation of the herniated contents, which can threaten the life of the patient if diagnosis is delayed [1]. We reported a late case of diaphragmatic hernia complicated with intestinal obstruction with colon perforation after esophagectomy which diagnosis was delayed and discuss how to prevent and treat this complication.

## Case report

A 65-year-old male patient, who had squamous cell carcinoma of esophagus underwent Sweet esophagectomy with gastric pulled-up. Reconstruction was performed on aortic arch in left thoracic cavity. Eight months after operation, the patient had felt abdominal distension and stopped defecation and exhaust from anus for 10 days, with vomiting. Then he had been treated only with transfusion for 8 days in the clinic of countryside, but the symptoms didn't improved any more, and then chest CT scan was done which showed bowel loops and air-fluid levels in left hemithorax, considered left diaphragmatic hernia (Fig. 1 and 2). The patient was transferred to our hospital (Northern Jiangsu People's Hospital Affiliated to Yangzhou University, China) immediately.

Physical examination revealed the entire belly bulging, tenderness, no rebound tenderness and obvious decreased breath sounds on the left hemithorax. The emergency operation of left thoracotomy exploration was performed with posterolateral thoracotomy incision line. Large amounts of manure odor excretions effusions could be seen in thoracic cavity. Jejunum and flexura lienalis coli attached with its mesentery entered left thoracic cavity through a 4–5 cm diaphragmatic defect. There was an opening about 3 cm length on the middle section of colon transversum and an opening about 5 cm length on flexura lienalis coli. The transversum around opening was polluted serious and large pus formed. Therefore we cut off rib bow, extended incision to abdomen, rowed part transverse colon resection, and proximal end colon made mouth, distal colon closed, and diaphragmatic hiatus was repaired. Although severe pyothoracic and lung infection happened post-operation and Candida albicans was found in pleural fluid and sputum cultures, the patient recov-

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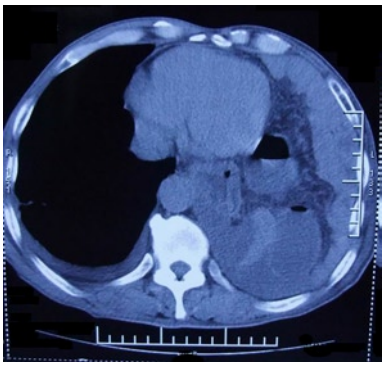

**Fig. 1** Transverse plane of computed tomography demonstrated bowel loops and air-fluid level in the left hemithorax

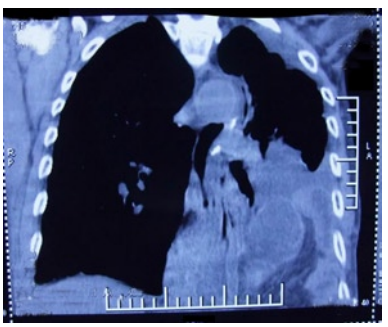

**Fig. 2** Vertical plane of computed tomography showed bowl loops in hemithorax and disappear of normal curve of diaphragm

ered and discharged with active treatment 35 days after operation. Colonic anastomosis operation was performed half a year later successfully.

## Discussion

Esophagectomy through left posterolateral thoracotomy is a standard surgical procedure for both benign and malignant esophageal diseases [2], especially for the distal lesion of esophagus. The mediastinal route is almost always used after esophagectomy in most hospital. Diaphragmatic hernia after surgery occurs only when mediastinal route is used. It is a rare but preventable postoperative complication that occurs in 0.4% to 4% of cases [3–5]. To present , about total of 30 cases of diaphragmatic hernia after esophagectomy for esophageal cancer have been reported in the English-language literatures [3–10]. Among these cases only 1 case developed a diaphragmatic hernia with perforation of the large bowel in the left hemithorax [10].

The main cause of postoperative diaphragmatic hernia was extensive dissection of the esophageal hiatus during operations. Van Sandick concluded that the risk of diaphragmatic hernia after esophagectomy was significantly higher with extended iatrogenic enlargement of the hiatus than with routine hiatal opening [4]. At the end of the operation, the hiatal defect should always be inspected. If the defect is too wide, it should be partially stitched to 3 or 4 fingers of the hiatus [3]. Many authors recommended anchoring the stomach anteriorly to the hiatus [6, 9].

Difficulties in diagnosis were reported in nearly every case in the literatures. Mortality rates increased depending on the delay in diagnosis [1]. Strangulation or perforation of the herniated contents is the life-threatening factor. Chest X-ray examination and CT scan are the important examinations for confirmation of the diagnosis, which demonstrate: the level of diaphragmatic muscle in the trouble side rises, bowel loops and air-fluid levels are visible over the diaphragmatic muscle, heart and mediastinum shift to the healthy side, ipsilateral pulmonary collapse is observed in the trouble side. In this case, the conservative treatment of the patient took too long, which delayed the diagnosis and treatment and resulted in colon perforation.

The emergency operation of repairing diaphragmatic and hiatal defects should be done once final diagnosis confirmed. If the colon perforation is found, we may consider one-stage anastomosis while light pollution. But while pollution is serious, we should perform proximal end colon neostomy and the second phase colonic anastomosis operation several months later.

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# Chinese-German Journal of Clinical Oncology

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# Chinese-German Journal of Clinical Oncology

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