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July 2012 Volume 11 Number 7

Contents

Original Articles

Case Reports

Activities Report

Information

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Chinese-German
Journal of Clinical Oncology

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。

EMBASE是由Elsevier公司出品，Excerpta Medica（荷兰《医学文摘》）的在线版本。涵盖70个国家/地区出版的3800多种期刊，覆盖各种疾病和药物的信息。

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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Intrathoracic latissimus dorsi muscle transposition: a reliable technique for prevention of bronchopleural fistula developing after extrapleural pneumonectomy and external beam radiotherapy in malignant pleural mesothelioma

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Abstract ***Objective:*** Bronchopleural fistula (BPF) is a life threatening complication after pneumonectomy. Extra thoracic skeletal muscle transposition especially latissimus dorsi muscle flap (LDMF) had been used to prevent this complication. The aim of this study was to assess the effectiveness of LDMF in preventing BPF developing after extrapleural pneumonectomy (EPP) and external radiation therapy in malignant pleural mesothelioma (MPM). ***Methods:*** Between May 1999 and Dec. 2008, 37 patients with MPM were operated upon by EPP using LDMF prophylactically to reinforce the bronchial stump, and then received external radiation therapy with or without postoperative chemotherapy. ***Results:*** The mean age of all patients was 46.7 (range 26–57) years. Twenty five patients were males and 12 patients were females. Twenty three patients had MPM of the right side and 14 patients had MPM of the left side. The peri-operative mortality was 2.7% and only few flap related postoperative morbidity were reported in the form of minor seroma and subcutaneous surgical emphysema. The median follow up was 17 (range 9–43) months. All cases completed their postoperative external radiation therapy with no reported cases of early or late BPF. ***Conclusion:*** Intrathoracic pedicled LDMF transposition is proved to be effective in prevention of BPF developing after EPP and external radiation therapy in MPM and it is advised to be a routine step in EPP in these cases and to use more sophisticated technique of postoperative external beam radiotherapy (3D conformal or IMRT) to minimize this complication.

Key words malignant pleural mesothelioma (MPM); extrapleural pneumonectomy (EPP); latissimus dorsi muscle flap (LDMF); bronchopleural fistula (BPF)

Single modality treatment for malignant pleural mesothelioma (MPM), whether chemotherapy, radiation therapy or surgery was unable to prolong life by more than several months at best thus combined modality approaches were advised to improve the efficacy of treatment [1, 2]. The best results were achieved by combination of extrapleural pneumonectomy (EPP) with sequential postoperative chemotherapy and external radiation therapy. Patients who had epithelial mesothelioma and no mediastinal lymph node involvement at resection had a remarkable 5-year survival rate of 39% when treated with this combination of treatment modalities [1, 3, 4]. Patients with sarcomatous tumors or tumors with mixed histologic findings had 2- and 5-year survival rates of 20% and 0%, respectively.

We started to treat MPM by EPP in our institute (Department of Surgical Oncology, National Cancer Institute, Cairo University, Egypt) since 1996 [5]. In 1997 we started a protocol to treat MPM with EPP followed by external beam radiation therapy. The incidence of bronchopleural fistula (BPF) was high (33.3%) after this combination of treatment with high mortality rate of this complication (75%), so we did a modification of the technique of the operation to preserve the latissimus dorsi muscle during thoracotomy and use it as a pedicled flap to cover the bronchial stump. We prospectively followed up these cases to assess the effectiveness of this technique to prevent the development of early or late BPF after EPP followed

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by external beam radiation therapy, there were several approaches to integrate external beam radiotherapy post-operatively but the approach with the highest local control rate was that using high dose of irradiation reaching 50–54 Gy.

Patients and methods

The criteria determining eligibility for EPP in our study included: Age < 65 years, good performance state (PS) grade 1 according to Eastern Co-operative Oncology Group (ECOG) scale system, but stage I MPM determined by chest CT scan, forced expiratory volume in 1 second (FEV1) greater than 2 L or predicted post-operative FEV1 greater than 1 L, preoperative partial pressure of CO_2 < 45 mmHg or a room air O_2 partial pressure > 55 mmHg, normal echocardiogram, normal kidney and hepatic functions and no previous pleural surgery e.g. partial pleurectomy.

Surgical technique

Our technique of EPP was similar to that described by Sugarbaker *et al* [6] but with some modifications. In the first of our study we used the standard posterolateral thoracotomy incision. At first we used to preserve the serratus anterior muscle but we cut the latissimus dorsi muscle. Later on we preserved both muscles. The anterior border of the latissimus dorsi muscle was identified. Superior and inferior subcutaneous flaps were raised superficial to the muscle fascia extending to its anterior and posterior borders. Dissection was started caudally to detach the muscle from its origin to ensure adequate length for proper tension free insertion within the thoracic cavity as excessive amount of shortening may occur once the muscle was released from its origin, then dissection was done towards the insertion of the muscle to identify the vascular pedicle of the flap and if effective length was needed the arc of rotation of the muscle was increased by cutting the muscle insertion. The thoracodorsal nerve was cut to avoid contraction of the muscle and traction on the bronchial stump. The muscle was then wrapped in a moist laparotomy pad to be used for transposition later on. The average time for harvesting the entire flap was approximately 30 min.

Closure of the bronchial stump was done manually in all cases. Long bronchial stumps were avoided. We put an atraumatic clamp distal to the line of division. The bronchus was sharply divided and bleeding on the divided margin was managed either by ligation or clip application of the bronchial arteries avoiding the use of diathermy electrocoagulation. The membranous wall was approximated to the cartilaginous wall with interrupted Prolene 3–0 avoiding tying of any sutures along the lateral side of the bronchus. The bronchial stump was submersed into warm physiologic saline to detect possible air leaks that were secured with additional interrupted sutures.

Systematic mediastinal lymph node dissection or sampling was performed in all cases. Paraesophageal, peri-diaphragmatic, and subcarinal nodal stations were examined for tumors located on the right or left side. Paratracheal nodes were examined for right-sided tumors, whereas aorto-pulmonary window and para-aortic nodes were examined for left sided tumors. The median number of dissected mediastinal lymph nodes was 9 (range: 3–24 nodes), while the median number of dissected hilar lymph nodes was 5 (range: 2–10 nodes). Mediastinal and/or hilar nodes were positive in 21 cases. Hilar nodes were positive in 8 cases. In one patient only the hilar nodes were positive while in the other 7 cases both hilar and mediastinal nodes were positive. The median number of positive mediastinal nodes was 2 (range: 1–7 nodes) and the median number of positive hilar nodes was 2 (range: 1–3 nodes).

At the completion of the EPP, counter incision was used to make a window in the 3rd intercostal space to transpose the latissimus dorsi muscle flap (LDMF) into the thoracic cavity taking care not to twist or apply undue tension on the vascular pedicle. The muscle was loosely tacked to cover the bronchial stump with several interrupted 3–0 vicryl sutures. The muscle donor site was closed into layers over two large pore (18 Fr) closed suction drains. Drains were frequently removed after 5–8 days. We routinely used one intercostal chest tube which was usually removed after 48 hours (Fig. 1).

Postoperative management

Postoperatively, patients were managed in the Intensive Care Unit (ICU). They were monitored for vital signs, respiratory rate, and oxygen saturation by continuous oximetry. Patients were placed on bed rest for 48 hours to facilitate mediastinal stabilization. The thoracic epidural catheter was used for the first 3 to 5 days to control pain and to help prevent atelectasis that may lead to respiratory compromise. A fluid restriction was enforced to prevent pulmonary edema. Desaturation of oxygen levels was treated with a combination of diuresis, chest physiotherapy, and bronchoscopy if required. Daily chest radiographs were routinely performed. To prevent aspiration, oral intake was not begun until there was clear evidence of gastric function (Fig. 2).

Management of BPF

If BPF was suspected a thoracic CT-scan and bronchoscopy were performed. Cultures from postpneumonectomy cavity & sputum were taken. Closed chest tube drainage was immediately performed. A 36 Fr chest tube was put and re-exploration was done once diagnosis was confirmed. Re-exploration was done through the previous thoracotomy incision followed by debridement and

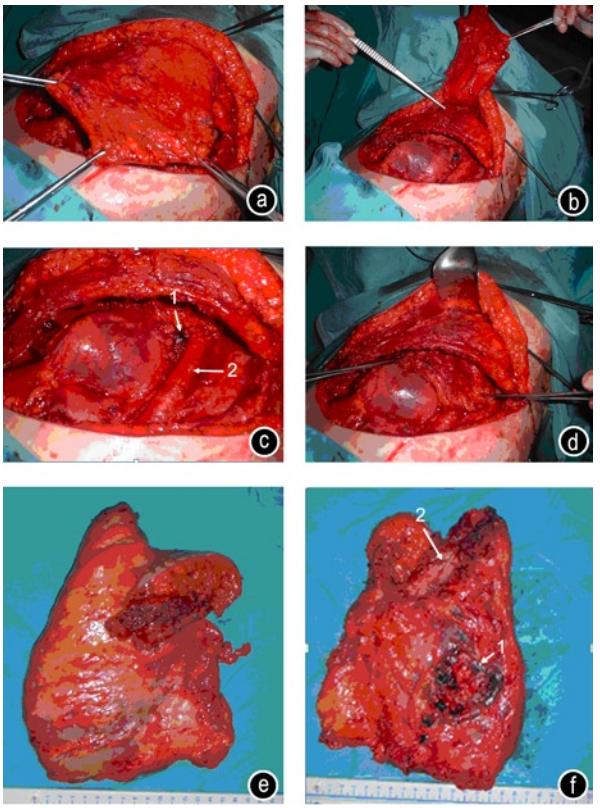

Fig. 1 (a) Latissimus muscle was preserved during the posterolateral thoracotomy; (b) Latissimus muscle flap was retracted cephalad and a window was formed in the 3rd intercostal space; (c) Operative view after left EPP showing: 1, hilar structures; 2, descending aorta; (d) The latissimus muscle flap was passed through the window and used to cover the bronchial stump; (e) Costal surface of the left EPP specimen showing en-block resection with the previous biopsy scar; (f) Mediastinal surface of the same specimen showing: 1, hilar structures (opened main bronchus and tied pulmonary vessels); 2, diaphragmatic muscle

identification of the BPF. Trimming of the edge of the bronchial stump was done with closure with multiple interrupted 3–0 Prolene sutures augmented with pedicled serratus anterior muscle flap. A chest wall window was performed after resection of 2 segments of adjacent ribs.

Postoperative radiotherapy

Postoperative radiotherapy was administered 4–6 weeks after EPP. A dose of 5000 cGy was given to the tumor bed and ipsilateral supraclavicular area divided into 25 fractions in 5 weeks (200 cGy/fraction) using 6 MV photon beam, and separate electron beam field was used in 22 cases to a dose of 50 Gy over 25 fractions over 5 weeks using energy ranging from 6 to 12 Mev to include the remaining part of the scare which was not included in the photon field.

Field margins

Upper border: C7–D1 to cover the supraclavicular area. Lower border: 2 cm below level of left cupola of the diaphragm in left sided lesions. On right sided lesions, liver was shielded from the start and the cupola of the diaphragm was irradiated by electrons after calculating the depth with CT scan. Medial border: Off cord i.e. 0.5–1 cm towards the surgery site to avoid spinal cord irradiation except in cases with positive mediastinal lymph nodes in which the mediastinum was irradiated and the cord dose was kept at 4000 cGy in 4 weeks. Lateral border: Lateral border encompassed the thoracic cage with a margin of 1 cm. An added separate electron beam field was used for the operative scar or drain sites.

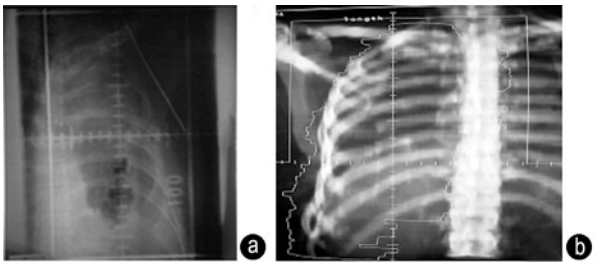

Fig. 2 (a) Check film for left hemi thora plane; (b) Anterior projection of a typical field encompassing the right hemithorax

Postoperative chemotherapy

It was started within 12–14 weeks after surgery in 23 patients were given every 3 weeks for 6 cycles, 15 patients received holoxan and adriamycin, and 8 received gem and cisplat.

Results

We started surgical treatment of MPM in our Institute since 1996. Between Jan. 1996 and May 1999, 43 patients fulfilled our criteria of EPP however EPP was done only in 29 patients (Group A). Six patients refused the operation and in 11 patients the tumor was limited and could be completely excised with less radical procedures. The perioperative mortality (within 30 days postoperatively) in Group A was 13.8% (4/29). The causes of intraoperative and early postoperative mortality were excessive intraoperative bleeding (2 cases), cardiac herniation (1 case), pneumonia of the other lung (1 case). One case developed BPF 6 weeks after right EPP and the patient developed severe aspiration pneumonia. Chest tube was inserted but the patient developed respiratory failure and put on mechanical ventilation and with selective intubation of the left lung and the patient died after 5 days. Other major complications were encountered in 4 patients but could be managed properly. Three cases developed atrial arrhythmia while one case developed BPF. The latter case presented with BPF after 8 weeks from left EPP. Chest tube was inserted then re-exploration was done with proper debridement of the necrotic tissues and Prolen mesh re-

Table 1 Incidence of BPF after EPP in relation to side of tumor and postoperative radiotherapy

	Frequency of Group A (13 cases + 12 cases)		Frequency of Group B (36 cases)
	EPP alone*	EPP + external radiotherapy	EPP with pedicled LDMF + external radiotherapy
Right-sided tumor	9	9	22
Right BPF (*n*)	1	4	0
BPF (%)	11.1	44.4	0
Left-sided tumor	4	3	14
Left BPF (*n*)	1	0	0
BPF (%)	25	0	0
Total (*n*)	13*	12	36**

* EPP alone was done in 17 cases. Four cases with early perioperative mortality (within one week) were excluded; ** EPP with pedicled LDMF was done in 37 cases. One case died in the early postoperative period and did not receive postoperative radiotherapy excluded; i. e. The total number of patients who received postoperative external beam radiotherapy was 48 cases

moval then bronchial closure was done with reinforcement with serratus anterior muscle flap. In 12 patients of Group A, external beam radiation therapy was given after EPP. The incidence of BPF after EPP alone and after EPP and radiotherapy was presented in Table 1.

The overall incidence of BPF in Group A was 24% (6/25) after excluding the 4 cases that died intraoperatively or in the early postoperative period. While the incidence of BPF was 15.4% after EPP alone (2/13) it was 44.4% in the group that undergone right EPP and postoperative external radiation therapy (4/9). In these 4 cases chest tubes were immediately inserted and proper antibiotics were given. One patient developed severe pneumonia and died while the remaining 3 patients were re-explored with reclosure of the bronchial stump and reinforcement with pedicled serratus anterior muscle flaps. Only one patient survived while the other 2 patients developed respiratory failure and were put on ventilatory support. They died 2 and 5 days after the re-exploration. To avoid this fatal complication we modified our surgical technique with preservation of the latissimus dorsi muscle during thoracotomy then using it as a pedicled flap to cover the bronchial stump as a prophylactic measure of BPF. Between May 1999 and December 2008, 37 patients underwent EPP using this modification (Group B). One patient developed postoperative pulmonary edema and pneumonia of the contralateral lung and died on the 8th postoperative day. The remaining 36 cases developed only minor flap related complications in the form of minor seroma and subcutaneous surgical emphysema in 8 cases. The alive 36 cases in Group B received postoperative radiotherapy and 23 patients received postoperative chemotherapy. The median follow up of our cases in Group B was 17 (range 9–43) months. All cases completed their postoperative external radiation therapy with no reported cases of early or late BPF.

Regarding radiotherapy induced acute toxicity it was found that all patients developed grades 2–3 oesophagitis which was easily managed and 80% of patients developed dry skin desquamation while 20% developed wet desquamation of the skin included in the radiation fields which was treated easily without delay.

Discussion

Pleural mesothelioma is a rare fatal disease which is mainly related to asbestos exposure [7–9]. The majority of MPM cases in our study (92.5%) were born or living in Elmaasara, Shobra Elkhema, Elhwamdia, and Hadayek Helwan. The above data are explained by the fact that these areas lie in the vicinity of factories that were using asbestos in industry till the early years in the last decade in our country. Although the Egyptian Minister of Foreign Trade and Industry prohibited the import and manufacture of all types of asbestos and asbestos materials in 2006 [10], we expect to face many new cases with MPM for further 30–40 years (the latency period between exposure to asbestos and developing the disease). So the trials to reach the best management of this fatal disease should not be stopped.

Multimodality therapy is still the hope in the management of MPM. Chemotherapy and radiation therapy alone cannot deal with the bulk of the disease, although they may play a role as adjuvant therapy. EPP facilitates giving postoperative radiation therapy at high doses especially if done with our new technique using pedicled LDMF.

The mortality rates following EPP were unacceptably high in the 1970s, with a 31% mortality reported by Butchart *et al* [11]. In a prospective multi-institutional study, the mortality rate was 15% [12]. However, single institution retrospective studies in which patients had been carefully selected reported lower mortality rates. Rusch and Venkatraman [13] reported a perioperative mortality of 6% (3/50) after EPP and Grondin and Sugarbaker [14] reported a perioperative mortality of 3.8% (7/183) after EPP. In our study the perioperative mortality rate in the 1st 29 patients (Group A) was high 13.8% (4/29). The causes were theoretically preventable including 2 cases of intraoperative hemorrhage, one case of left cardiac

herniation and one case of pneumonia of the other lung. The perioperative mortality in the following 37 patients (Group B) was 2.7% with only one mortality in the early postoperative period due to pulmonary edema and chest infection of the contra-lateral lung.

Good monitoring of patients during EPP is mandatory with adequate blood replacement when indicated to avoid irreversible shock. At first we used to repair large pericardial defects on the right side only but later on we repaired large pericardial defects whether on the right or left sides by a permeable mesh. It is reported in the literature that cardiac herniation is rare in the left side and that there is no need to repair large left pericardial defects. However, we lost a patient because of cardiac herniation on the left side which occurred immediately postoperatively. Upon turning the patient on his back sudden arrest occurred. Immediate re-exploration was done, the patient was resuscitated, and the pericardial defect was repaired with Prolene mesh. Unfortunately the patient did not recover and died 3 hours after the operation. Patients should be examined carefully preoperatively for the possibility of mitral valve disease. Fluid balance should be monitored carefully intraoperatively, and in the postoperative period to avoid the risk of pulmonary edema.

BPF is a life threatening septic and ventilatory catastrophe after pneumonectomy. The reported incidence of postoperative BPF varied from 0.8% to 28% [15–21]. The reported incidence of BPF after EPP in MPM was 3%–20% [22]. Many risk factors are claimed to increase the incidence of BPF after pneumonectomy including, right sided pneumonectomy, preoperative chemotherapy and/ or radiotherapy, postoperative radiotherapy, preoperative infection, postoperative mechanical ventilation, postoperative pneumonia , presence of underlying lung diseases, poor predicted post-pneumonectomy forced expiratory volume in 1 second, long bronchial stump, extended resection, disrupted bronchial blood supply, tumor at bronchial stump margin, chronic malnutrition, perioperative transfusion, insulin dependent diabetes and old age [16–21, 23–25].

In our study the overall incidence of BPF in the group that undergone EPP without LDMF (Group A) was 24% (6/25) after excluding the 4 cases that died intraoperatively or in the immediate postoperative period. While the incidence of BPF was 15.4% after EPP alone (2/13) it was 44.4% in the group that undergone right EPP and postoperative external radiation therapy (4/9). In the group that undergone EPP with prophylactic LDMF (Group B), apart from the case that died in the early postoperative period, all other cases completed their postoperative external radiation therapy with no reported cases of early or late BPF. Many years ago, Sweet [26] emphasizes the principles of bronchial closure including minimal bronchial trauma, preservation of blood supply to the cut end and adequate tissue reinforcement of the bronchial suture line. There is still controversy about the best type of bronchial closure whether to use the manual or mechanical method. Some surgeons report a low percentage of fistulas developed by manual closure [18], while others reported that mechanical staplers were superior to manual closure [23]. Manual closure may be at least as good as stapled closure [24, 27] but more important, it can always be performed in cases when stapled closure is difficult or should be avoided [27, 28]. The stapler is difficult to apply when the bronchial wall is hard due to calcification of the cartilage or when massive hilar lymphadenopathy co-exist [29] and it is contraindicated when the bronchus is thickened, inflamed or of insufficient length [28]. In our study all cases of bronchial closure was done by manual closure using interrupted Prolene 3/0 sutures. Sweet principles of bronchial closure were respected [26]. Using the LDMF as reinforcement to the bronchial stump suture line in Group B was effective in preventing early or late BPF in all cases.

The occurrence of BPF is still associated with high mortality rates ranging from 25% to 71.2% and the most common cause of death is aspiration pneumonia with subsequent acute respiratory distress syndrome (ARDS) [17, 19, 24]. Mortality of BPF is higher after right pneumonectomy 44% than left pneumonectomy 33% [20]. Postoperative BPF is divided into early and late according to the time of occurrence. Early BPF occurs within a month after the operation [21]. Early BPF is more dangerous than late BPF. The incidence of aspiration pneumonia declines sharply if BPF occurs more than 3 months after operation. Formation of fibrothorax apparently represents a natural protection against fistula formation and subsequent fatal aspiration pneumonia [24, 30]. In our study BPF developed in 6 patients with high mortality rate of 66.6% (4/6).

To prevent postpneumonectomy BPF, coverage of the bronchial stump is recommended in patients with possible risk factors especially for patients treated with neoadjuvant and/ or adjuvant chemotherapy or radiochemotherapy [15, 27, 31]. There is still controversy about the indications and different techniques of bronchial stump coverage to prevent postoperative BPF. Many surgeons prefer to cover all stumps after right pneumonectomies [23, 24]. In left sided pneumonectomies the bronchial stump retracts and is covered by the aorta and surrounding tissues thus some surgeons recommend to leave the left side stump uncovered except for high risk patients where closure of the bronchus was performed manually [23], however, others advocate the need for routine coverage on the left side as well [18, 32].

A great variety of tissues has been used for bronchial stump reinforcement using both intra- or extra-thoracic tissues. Intra-thoracic tissues include the parietal pleura, pericardium, intercostal muscles and diaphragmatic flaps [15, 33–35]. Intrathoracic transposition of an extrathoracic

muscle to buttress repair of BPF was first described in 1911 by Abrashanoff [36]. For many decades following, extrathoracic muscle flap transposition has been utilized to obliterate potential pleural space problems especially of chronic infections and to reinforce bronchial stumps for prevention or treatment of BPF. The chest wall skeletal muscles most frequently used have been latissimus dorsi, serratus anterior and pectoralis major muscles [25, 37–40]. Other extrathoracic pedicled flaps included the pedicled rectus abdominis muscle and the pedicled omentum [37, 41].

In MPM some flaps are not suitable for bronchial stump reinforcement. Pleura is involved by the tumor and resected. The pericardium may be also involved by the tumor and may be resected. Extrapleural dissection preserving an intact well vascularized intercostal muscle flap is problematic. The azygos vein flap was used in 3 cases out of the 5 cases of right EPP who developed BPF in our study and not effective in preventing the development of BPF. The pedicled LDMF is the most commonly used chest wall skeletal muscle as it can be sacrificed without affecting much the patient's shoulder or arm function while serratus anterior and pectoralis major muscles are not entirely expendable. Sacrificing the serratus anterior muscle will lead to winging of the scapula and inability to elevate the arm above the horizontal plane [38] while sacrificing the pectoralis major muscle will lead to loss of the anterior axillary fold and subsequent contour deformity of the chest wall [38]. The pedicled rectus abdominis and omentum are less suitable than the pedicled LDMF because they require separate abdominal wound and may lead to hernia formation, deformity of the abdominal wall or abdominal spread of the tumor.

Although BPF is more common after right EPP, we routinely used the prophylactic pedicled LDMF for augmentation of the bronchial stump after right or left EPP considering the minor complications of this technique and the difficult management of BPF with high fatality rate.

Conclusions

EPP can be done safely with low mortality and morbidity in selected patients. Old aged patients, those with cardiac problems, and those with poor respiratory functions which do not improve after intercostal tube is put, should be excluded of EPP. A main item in the safety of EPP is the co-operation between anesthetic and surgical teams. The postoperative period is critical and patients should be closely monitored and if complications develop they should be properly managed. Prophylactic pedicled LDMF after EPP is a safe reliable technique to prevent BPF with minor complications, also it is recommended to use more sophisticated technique of external beam radiotherapy (3D conformal or IMRT) for proper shielding for the bronchial stump to minimize this complication also to allow safe completeness of adjuvant radiotherapy.

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Empirical studies about quercetin increasing chemosensitivity on human lung adenocarcinoma cell line A549*

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Abstract ***Objective:*** The present study was designed to investigate whether quercetin exerts increasing chemosensitivity on human lung adenocarcinoma cells when quercetin combined with cisplatin (DDP) and vincristine (VCR) *in vitro* respectively and its possible antitumor mechanism. To provide experimental proof for clinical combination application. ***Methods:*** Using intermittent administration of high dose VCR, human lung adenocarcinoma sensitive cell line (A549/S) was induced to VCR-resistant human lung adenocarcinoma cell line (A549/VCR). MTT assay was adapted for examing the 50% inhibition (IC_{50}) value of DDP and VCR on A549/S and A549/VCR when quercetin combined with DDP and VCR respectively. ***Results:*** IC_{50} of DDP on A549/S and A549/VCR was 10.18 and 12.35 mg/L, and the IC_{50} of VCR on the two cell lines was 1.21 and 12.77 mg/L, respectively. The resistance fold of A549/VCR on VCR and DDP was 10.55 and 1.21, respectively. When quercetin at concentration of 50, 100 and 200 μmol/L in combination with DDP and VCR respectively, the IC_{50} of DDP and VCR on A549/S and A549/VCR were obvious decreased ($P < 0.05 – P < 0.01$). ***Conclusion:*** The experiment results suggested that quercetin could increase the chemosensitivity and partly revise the resistance of A549/VCR.

Key words quercetin (Que); A549 lung adenocarcinoma cell line; cisplatin (DDP); vincristine (VCR); increase chemosensitivity

Quercetin (Que) distribute widely fruit, vegetable, beverage, tea and various Chinese herbal medicine. It has definite multiple biological activities and pharmacological actions including to dilate coronary artery, reduce blood-lipid, anti-platelet aggregation, anti-oxidization and free radicle removing, anti-inflamation, ananaphylaxis and so on [1, 2]. Besides, Que is known as yet to be one of the most powerful effective ingredient of anti-cancer Chinese medicine [3]. Lung cancer is the incidence higher of respiratory tract tumor in China. Chemotherapy is one of the majory treatment for lung cancer. But failure of chemotherapy greatly results from the resistance against chemotherapeutic reagents in lung cancer cells. The purpose of the experiment is to observate the effects of Que combination two chemotherapeutics [cisplatin (DDP) or vincristine (VCR)] on human lung adenocarcinoma sensitive cell line (A549/S) and VCR resistant cell line (A549/VCR), and investigate whether Que increase the chemosensitivity of A549 adenocarcinoma cells *in vitro*.

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Materials and methods

Reagents and instruments

PRMI 1640 medium was purchased from Hydone USA.; bovine calf serum (Fcs) from Sijiqing Bioengineering Co. Ltd. (China); Que from Jiukang Chemical industry Co. Ltd. (China); VCR sulfate for injection from Haizheng Pharmaceutical Co. Ltd. (China); DDP injection from Gejiu Pharmaceutical Co. Ltd. (China); methyl thiazolyl tetrazolium (MTT) from Junyao Bio-technology Co. Ltd. (China); 96-wells tissue culture plate from JET Biochemicals Int'I., Inc. (Canada); Dimethylsulfoxide (DMSO) from Shanghai. ST-36 ELISA Reader from Shanghai; Model 6000 water jacket CO_2 incubator from USA.

Tumor cells culture and establishment of resistance cell line

Human lung adenocarcinoma sensitive cell line (A549/S) was gifted from Professor Keng Yuan of Jiangxi Institute of Medical Science, China.

A549/S cells were subcultured in PRMI 1640 medium with 10% Fcs, penicilin 1.0×10^5 U/L, streptomycin 100 mg/L and maintained in a 5% CO_2 atmosphere at 37 ℃ with 95% humidity after the cells recovered. The cells were divided bottles subcultured after trypsinization when the cells grew well.

A549/S was induced to vincristine-resistant cell line (A549/VCR) by using intermittent administration of high dose VCR [4]. When A549/S cells were in the logarithmic growth phase, VCR was added to the medium to a final concentration of 5 mg/L. After one h incubation, supernatants of containing VCR were discarded. Centrifugation (1000 rpm/min) for collecting cells and adjust cells number to 1.0×10^6 /L after 0.25% trypsinization. The cells were anew suspended in PRMI 1640 medium without VCR and continuing culture for several generations. When the cells grew well, the above-mentioned trails were replicated until the cells could be growth stably in 0.6 mg/L VCR complete medium and continual subculturing. The cell line was used for experiments after two weeks of culture in drug-free.

Increasing chemosensitivity of Que on A549/S and A549/VCR cell lines using MTT assay

Experiment grouping A549/S and A549/VCR cells suspension (1.0×10^8/L, 160 μL) in the logarithmic growth phase were inoculated in 96-well plate. After the cells were adherent, five groups were assigned.

(1) DDP group was treated with DDP at concentrations of 0.6, 1.5, 3.0 and 6.0 mg/L, respectively.

(2) Combined Que with DDP group was treated with Que and DDP. The final concentration of Que was 25, 50, 100 and 200 μmol/L, respectively and concentration of DDP was the same as DDP group.

(3) VCR group was treated with VCR at concentrations of 1.0, 3.0, 5.0 and 10.0 mg/L, respectively.

(4) Combined Que with VCR group was treated with Que and VCR. The final concentration of Que was the same as combined Que with DDP group and concentration of VCR was the same as VCR group.

(5) Tumor cell control group was treated with PRMI 1640 medium.

Three parallel bores were designed in each concentration of the above every group. PRMI 1640 medium that the tumor cells had not been inoculated was added in adjustment zero bore.

Above every group cells were incubated maintaining in a 5% CO_2 atmosphere at 37 ℃ with 95% humidity. After 68 hours, 20 μL MTT (5 mg/L) was added each bore for 4-h incubation. Then 150 μL DMSO was added. The plate was oscillated for 10 min by micro-oscillator in order to dissolve formazan fully.

The optical density at 570 nm (OD_{570}) were measured using a ELISA Reader. IC_{50} was calculated according as linear regression equation.

Cells growth inhibition rate = 1 – [(Drug bore OD value – adjustment zero bore OD value) / (Control bore OD value – adjustment zero bore OD value)].

Increasing chemosensitivity fold = IC_{50} of chemotherapeutic group / IC_{50} of (Que + chemotherapeutic group).

Statistical analysis

The significance of difference between chemotherapeutic group and combined Que with chemotherapeutic group was determined by the coverage *t*-test using the SPSS 11.5 software. A value of $P < 0.05$ was considered significant.

Results

Establishment of VCR resistance cell line (A549/VCR)

A VCR-resistance cell line A549/VCR (resistant to VCR 0.6 mg/L) was established by intermittent administration of high dose VCR after 6 months. The VCR-resistant cell line (A549/VCR) could long subcultured maintaining in 0.6 mg/L VCR and the cells grew well. The resistance fold of A549/VCR to VCR and DDP was 10.55 and 1.21, respectively.

Que increasing the chemosensitivity of A549/S and A549/VCR cell lines

According to the results of MTT assay, Que in different concentration could decreased IC_{50} value of DDP on A549/S and A549/VCR (Table 1), VCR on the two cell lines in varying degrees, respectively (Table 2). There was no significant difference of the increasing chemosensitivity folds between Que on A549/S and A549/VCR when Que of difference concentration combined with DDP ($P > 0.05$; Table 1). But the increasing chemosensitivity fold of Que on A549/S was significantly higher than A549/VCR when Que at concentration of 50, 100, 200 μmol/L combined with VCR ($P < 0.05$ – $P < 0.01$; Table 2).

Discussion

Small molecular natural compounds have been a hot topic of anti-tumor research in home and abroad. As natural small molecular flavonoid drug, Que has positive anti-tumor effects as others flavonoids drugs, for instance, casticin and celastrus orbiculatus thunb [1, 5, 6]. In recent years scholars of domestic and abroad have a lot of researched about Que anti-tumor. The research show that Que has not only chemopreventive effect on tumor [7], but also to inhibit the proliferation of human various tumor cells [8, 9]. Que can to promote differentiation of tumor cells [10] and induce the cells apoptosis [11]. Que also able revise multidrug resistance of the resistant tumor cells [1, 12]. There is a

Table 1 Comparing with IC_{50} value (mg/L) between DDP group and combined Que with DDP group

Cell line		DDP group	Combined Que with DDP group			
			Que 25 μmol/L	Que 50 μmol/L	Que 100 μmol/L	Que 200 μmol/L
A549/S	DDP IC_{50} value	10.18 ± 1.77	8.47 ± 1.72△	5.04 ± 0.14★	3.13 ± 0.18★	2.66 ± 0.78*
	Increasing sensitivity fold		1.20	2.02	3.25	3.83
A549/VCR	DDP IC_{50} value	12.35 ± 0.50	10.89 ± 1.17△	5.84 ± 0.65*	3.71 ± 0.97*	3.19 ± 0.33*
	Increasing sensitivity fold		1.13△	2.11△	3.33△	3.87

Combined Que with DDP group vs DDP group: △ $P > 0.05$, ★ $P < 0.05$, * $P < 0.01$; comparing with increasing sensitivity folds, Que to A549/VCR vs Que to A549/S: △ $P > 0.05$

Table 2 Comparing with IC_{50} value (mg/L) between VCR group and combined Que with VCR group

Cell line		VCR group	Combined Que with VCP group			
			Que 25 μmol/L	Que 50 μmol/L	Que 100 μmol/L	Que 200 μmol/L
A549/S	VCR IC_{50} value	1.21 ± 0.25	0.93 ± 0.13△	0.51 ± 0.10★	0.38 ± 0.09★	0.28 ± 0.08*
	Increasing sensitivity fold		1.30	2.37	3.18	4.32
A549/VCR	VCR IC_{50} value	12.77 ± 0.35	10.53 ± 0.77△	7.34 ± 0.64*	5.45 ± 0.72*	4.15 ± 0.24*
	Increasing sensitivity fold		1.21△	1.74★	2.34*	3.08*

Combined Que with VCR group vs VCR group: △ $P > 0.05$, ★ $P < 0.05$, * $P < 0.01$; comparing with increasing sensitivity folds, Que to A549/VCR vs Que to A549/S: △ $P > 0.05$, ★ $P < 0.05$, * $P < 0.01$

synergistic effect when Que combined with chemotherapeutic drugs to treat tumor [13].

In this study the increasing the chemosensitivity of Que on A549/S and A549/VCR cell lines is assayed by MTT when Que combined with DDP or VCR. The research results show there were significant differences between the IC_{50} value of DDP group and combined Que with DDP group on A549/S and A549/VCR, VCR group and combined Que with VCR group on the two cell lines when Que at concentration of 50, 100, 200 μmol/L combined with DDP and VCR, respectively ($P < 0.05 - P < 0.01$). The experiment results suggest that Que can increasing chemosensitivity of DDP and VCR on the two cell lines. Its increasing sensitivity effect is in dose-dependent manner. And Que can partly revised resistance of A549/VCR by the increasing chemosensitivity of Que on the resistant cell line.

DDP and VCR are conventional chemotherapeutic drugs of clinical treatment for tumor. The two drugs have a certain effective for middle and later period tumor. But there are some toxicity and side-effects including alimentary reaction, kidney toxicity, inhibiting marrow and acoustic nerve damage, etc [14, 15]. And the toxicity and side-effects are related to the drugs dose. This study reveals that the doses of DDP and VCR can be decreased when Que combine with DDP or VCR. Thereby the toxicity and side-effects of the drugs are reduced.

The possible mechanisms of the increasing chemosensitivity of Que on tumor cells are to make that tumor cells stay in cell cycle of chemotherapy sensitivity; degradation rate of drugs *in vivo* and cells are reduced; it has increased to uptake rate and target distribution of drugs to tumor tissue; it has also enhanced to resist of normal tissue to side-effect of drugs [16].

Because of the resource of Que is abundant and has both various biological activities and pharmacological actions. As the drugs of anti-cardiovascular disease, Que has been applied in clinic. Its toxicity is a little whether oral or intravenous injection. Que protects renal tubular epithelial cells from damage toxicity *in vitro* [17]. Hence it may be applied to chemotherapy of tumor when Que combines with chemotherapeutic drugs and has extensive application foreground and development values. But at present the most researches about Que anti-tumor have only staied in cell and animal experiment stage, and results of clinical study are minority. Besides, the oral absorb rate is influenced because its water-soluble is shortage. So in order to enhance the oral absorb rate of Que , it seems to be particularly important to increase its polarity by improving biological conformation of Que. It still need further study about the molecular mechanism of the combination of Que and chemotherapeutic drugs anti-tumor effects.

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Effect of radical surgery combined with pre- or postoperative radiotherapy in treatment of resectable rectal cancer

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Abstract ***Objective:*** This study was done to compare between the effect of preoperative radiotherapy and postoperative radiotherapy in treatment of resectable rectal carcinoma. The primary endpoints are local recurrence rate, overall survival (OS) and disease free survival (DFS). The secondary endpoints are to evaluate down-staging, treatment toxicity, and ability to do sphincter preservation, aiming at choosing the optimal treatment modality. ***Methods:*** This study included 100 patients with resectable rectal carcinoma who presented to Surgical Gastro Entrology Center and Clinical Oncology and Nuclear Medicine Department, Mansoura University during the period between January 2007 and September 2009. The included patients were randomized in two groups; group I: 50 patients received preoperative radiotherapy and group II: 50 patients received post-operative radiotherapy. Concurrent 5-fluorouracil-based chemotherapy was given to all patients. Two major types of surgery were done: abdomino-perineal resection with a permanent colostomy and low anterior resection with colorectal or coloanal anastomosis. ***Results:*** Preoperative radiotherapy resulted in pathologic complete response in 3 patients. T down-staging occurred in 18 out of 50 patients (36%) with statistically significant difference (P = 0.008). N down-staging occurred in 10 out of 24 patients. Sphincter preservation was more in group I. Delayed wound healing was the most common postoperative complication in group I with no significant difference. After a median follow up of 18 months, local recurrence rate and distant metastasis were higher in group II. The 2-year disease free survival was 72% and 60% in group I and II respectively with no statistically significant difference between both groups. ***Conclusion:*** This study concluded that preoperative radiotherapy is better than postoperative radiotherapy as regard local control, sphincter preservation with higher disease free survival and overall survival. No difference in treatment toxicity between both groups.

Key words resectable rectal cancer; preoperative radiotherapy; postoperative radiotherapy

Over the past 25 years, advances have been made in the multimodality management of patients with resectable rectal cancer [1].

Until recently surgery had remained the primary treatment modality but in spite of curative resection a significant proportion of patients develop local recurrence (20%–50%) [2]. Loco-regional recurrence after resection of rectal cancer is difficult to treat and is associated with severe debilitating symptoms. The prognosis after a local recurrence is poor, with a median survival of 12–18 months [3].

The goal of using radiation therapy as an adjuvant treatment for rectal cancer is to prevent local recurrence with its associated morbidity and mortality [1]. There is a number of potential advantage of preoperative radiation therapy for resectable rectal cancer; decreasing tumor seeding at the time of surgery, increasing radiosensitivity due to more oxygenated cells, no post-surgical fixation of small bowel in the pelvis and down staging effect [4]. The major theoretical disadvantage of preoperative radiation therapy is possible over-treating 10% to 15% of patients, those with stages T1–2N0M0 who don't require adjuvant therapy [5].

An increase in tumor response and more sphincter preservation was demonstrated with preoperative radiation therapy in low rectal cancer [6, 7]. A lower incidence of side effects with preoperative versus postoperative radiotherapy was reported, with no evidence that postoperative radiotherapy improves survival [8].

The aim of this study was to compare the effect of preoperative and postoperative radiotherapy in management of resectable rectal carcinoma.

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The primary endpoint is local recurrence rate, overall survival (OS) and disease free survival (DFS). The secondary endpoint is to evaluate down-staging, treatment toxicity, and ability to do sphincter preservation, aiming at choosing the optimal treatment modality.

Patients and methods

This study included 100 patients with resectable rectal carcinoma who presented to Surgical Gastroenterology Center and Clinical Oncology and Nuclear Medicine Department, Mansoura University during the period between January 2007 and September 2009. These patients were randomly assigned in two groups:

Group I: 50 patients received preoperative radiotherapy of 45 Gy in 25 fractions followed by surgery (recommended to take place within 4–6 weeks of the last fraction of radiotherapy).

Group II: 50 patients received postoperative radiotherapy aiming at 45 Gy in 25 fractions in 5 weeks. Concurrent 5-fluorouracil (400 mg/m^2 IV bolus plus leucovorin 20 mg/m^2 IV bolus for 4 days at week 1 and 5 of radiotherapy) was given to all patients.

Eligible patients had histologically confirmed adenocarcinoma of the rectum (defined as the distal tumor less than 15 cm from the anal verge measured by recto-sigmoidoscopy) with no evidence of metastases (identified by abdominal CT scan and chest radiograph). The primary tumor had to be deemed resectable (defined as not fixed to the pelvis) as determined by digital rectal examination and preoperative abdomino-pelvic CT or MRI. Patients had Eastern Cooperative Oncology Group (ECOG) performance status (PS) score 0–1 and no history of previous chemotherapy or radiotherapy to the pelvis.

All patients were subjected to detailed clinical history, complete physical examination, laboratory tests (complete blood count, liver function tests, serum creatinine, CEA and CA19-9), endoscopy and pathologic examination of the biopsy. Patients were staged according to AJCC staging-2002.

Radiotherapy was given by high energy photon external beam irradiation, using Co-60 or linear accelerator (6 MV photons). The target volume was defined as the sacral promontory superiorly, 3–5 cm below the inferior tumor extent, and 1 cm lateral to the most lateral aspect of the bony true pelvis. The posterior border of the lateral field must include the whole sacral canal in the target volume, and the anterior border of the lateral field must be at the anterior border of the symphysis pubis. The perineal scar was to be included postoperatively in patients with tumors less than 5 cm from the anal verge.

Three to four weeks after the end of radiotherapy in group I, abdomino-pelvic CT or MRI was done with comparison to the pre-radiotherapy study.

Surgery

Two major types of surgery were done: abdominoperineal resection (APR) with a permanent colostomy and low anterior resection (LAR) with colorectal or usually colo-anal anastomosis. Down staging was defined as a reduction in T or N stage based on pretreatment clinical staging by CT or MRI versus final pathological staging.

Patients were followed up to record early postoperative mortality and morbidity such as delayed wound healing, anastomotic leakage, bleeding, ileus and fistula which occurred during hospitalization, or within 30 days of operative procedure.

After end of treatment

Patients were followed up for detection of local recurrence or late effect every 1–2 months by clinical examination, every 3 months by tumor markers (CEA & CA19-9), abdomino-pelvic CT or MRI and endoscopy, biopsies were taken and pathologically examined for suspicious lesion.

Statistical analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 15. Unpaired *t* test was used for comparison between different groups. Qualitative data were presented as number & percent. Chi-Square test was used for comparison between groups, as appropriate. Survival was compared using Kaplan-Meier method with Log-rank test of significance. $P \leq 0.05$ was considered to be statistically significant. Disease free survival (DFS) was calculated from the date of surgical resection till the date of recurrence (either local or distant) and overall survival (OS) was calculated from the date of diagnosis till the date of death.

Results

Table 1 showed patients characteristics of 100 patients. There was no difference in cross matching the 2 groups as regard age, sex, PS score, pathological types, site of tumor, presenting symptoms and tumor markers. There was a statistically significant difference regarding pathologic staging distribution ($P = 0.021$).

Regarding down-staging after preoperative radiotherapy, pathologic complete response (no detectable tumor in final histology) occurred in 3 patients without statistically significant difference ($P = 0.15$). T down-staging occurred in 18 out of 50 patients (36%) with statistically significant difference ($P = 0.008$). While N down-staging occurred in 10 out of 24 patients (whom there is positive lymph node at presentation) with highly significant difference.

Abdomino-pelvic CT or MRI, barium enema and endoscopy were diagnostic in 90.6%, 93.7% and 100% of patients respectively. CT scan or MRI findings were con-

Table 1 Patients' characteristics

Variable	Group I (preoperative RT)		Group II (postoperative RT)		*P* value
	n	%	*n*	%	
Age (years)					0.41
Range	20–75		22–80		
Median	48		45		
Gender					0.169
Male	34	68	27	54	
Female	16	32	23	46	
Male : female	2.1:1		1.2:1		
PS score					0.98
0	31	62	30	60	
1	19	38	20	40	
Symptoms*					0.734
Bleeding/rectum	43	86	40	80	
Constipation	24	48	27	54	
Abdominal pain	27	54	17	34	
Weight loss	19	38	20	40	
Other	12	24	8	16	
Site					0.043
Upper	0	0	3	6	
Middle	9	18	9	18	
Lower	41	82	38	76	
Pathologic cell type					0.809
Adenocarcinoma	24	48	27	54	
Mucinous	17	34	19	38	
Signet ring	9	18	4	8	
Pathologic stage					0.021
Stage 0: T0N0	3	6	0	0	
Stage I: T2N0	8	16	0	0	
Stage II: T3N1	19	38	21	42	
Stage III: T3N1	14	28	12	24	
T3N2	6	12	17	34	
Tumor marker					0.53
Normal levels	33	66	19	38	
CEA (> 5 ng/mL)	4	8	8	16	
CA19-9 (> 35 μg/mL)	4	8	19	38	
Both elevated	9	18	4	8	

* One patient may complain from more than one symptom

sistent with postoperative pathologic staging in 37.5% of patients, under-estimating and over-estimating the tumor stage in 6.2% and 43.7% of patients respectively; while it wasn't diagnostic in 6.9% of patients.

Regarding types of surgical procedures done in group I and II, APR was done in 31 (62%) and 45 (90%) patients respectively. Fifteen (31%) and 5 (10%) patients underwent low anterior resection in group I and II respectively. A statistically significant difference was found between both groups ($P = 0.011$), as more SSP and less APR were done in group I patients. Two patients in group I underwent palliative colostomy and another 2 patients underwent surgical exploration (Table 2).

Diverting colostomy was done in 5 patients in group I who underwent AR, closure of colostomy was done after the end of treatment, while resection anastomosis was done in 4 patients.

Postoperative surgical complications for both groups are illustrated in Table 3. Delayed wound healing was the most common toxicity observed in group I which occurred in 7 patients (14%), three patients developed

Table 2 Types of surgical procedures

Type of surgery	Group I		Group II		*P*
	n	%	*n*	%	
Abdomino-perineal resection (APR)	31	62	45	90	
Low anterior resection (LAR)	15	30	5	10	0.011
Palliative colostomy	2	4	0	0	
Exploration	2	4	0	0	

Table 3 Postoperative surgical complications

Event	Group I		Group II	
	n	%	*n*	%
Early				
Delayed wound healing	7	14	2	4
Renal complication	1	2	0	0
Anastomotic leakage	2	4	2	4
Intestinal obstruction	3	6	1	2
Late				
Urgency & frequency	1	2	1	2
Anastomotic stricture	2	4	3	6

adhesive intestinal obstruction, anastomotic leakage occurred in 2 patients and one patient developed renal complication.

Relation between recurrence and different prognostic factors is presented in Table 4. There was no statistically significant relation between patients' age, gender, tumor pathology, stage or type of surgery and disease recurrence in both groups. A statistically significant relation was found between site of tumor and recurrence in group II ($P = 0.045$), as lower third tumors had a higher tendency to recur. Also, patients who had elevation in both tumor markers (CEA & CA19-9) showed a higher rate of recurrence in group I ($P = 0.037$).

After a follow up period that ranged from 6–28 months for all patients, with a median of 18 months and a mean of (18.2 ± 4.8) months, we studied the patterns of recurrence. In group, 5 patients (10%) experienced local recurrence, while 6 patients (12%) developed distant metastases. The incidence of failure was higher in group II, where 16 patients (32%) experienced local recurrence, while 10 patients (20%) developed distant metastases. There was a statistically significant difference between both groups regarding local recurrence ($P = 0.031$), however; in respect to distant metastases in both groups, the difference was not statistically significant ($P = 0.083$; Table 5).

At the end of this study, there were 28 patients (56%) in group I and 14 patients (28%) in group II alive with no evidence of disease (NED). There were 8 patients (16%) in group I and 5 patients (10%) in group II alive with disease. There were 8 patients (16%) in group I and

Table 4 Relation between recurrence and different prognostic factors

Variable	Group I				*P*	Group II				*P*
	–ve		+ve			–ve		+ve		
	n	%	*n*	%		*n*	%	*n*	%	
Age (years)					0.390					0.426
< 40	16	32	0	0		10	20	3	6	
> 40	29	58	5	10		25	50	12	24	
Gender					0.753					0.554
Male	30	60	4	8		19	38	8	16	
Female	14	28	2	4		16	32	7	14	
Site of tumor					0.454					0.045
Upper	0		0	0		3	6	0		
Middle	7	14	2	4		8	16	1	2	
Lower	38	76	3	6		24	48	14	28	
Pathologic cell type					0.823					0.698
Adenocarcinoma	20	40	4	8		20	40	7	14	
Mucinous	15	30	2	4		14	28	5	10	
Signet ring	9	18	0	0		3	6	1	2	
Pathologic stage					0.534					0.139
Stage 0: T0N0	3	6	0	0		0	0	0	0	
Stage I: T2N0	8	16	0	0		0	0	0	0	
Stage II: T3N1	17	34	2	4		17	34	4	8	
Stage III: T3N1	12	24	2	4		7	14	5	10	
T3N2	5	10	1	2		10	20	7	14	
Tumor marker					0.037					0.823
Normal levels	30	60	3	6		17	34	2	4	
CEA (> 5 ng/mL)	4	8	0	0		5	10	3	6	
CA19-9 (> 35 μg/mL)	4	8	0	0		1	2	18	36	
Both elevated	4	8	5	10		2	4	2	4	
Surgical technique*					0.221					0.164
APR	26	52	5	10		30	60	15	30	
LAR	16	32	0	0		5	10	0	0	

P value ≤ 0.05 was considered statistically inoperable. * Three patients in group I were inoperable

Table 5 Disease recurrence

	Group I		Group II		*P*
	n	%	*n*	%	
Local recurrence	5	10	16	32	0.031
Distant metastasis					0.083
Liver	2	4	3	6	
Lung	2	4	2	4	
Bone	2	4	3	6	
Abdominal LN	0	0	2	4	

Table 6 Fate of patients at the end of follow up

Status	Group I		Group II	
	n	%	*n*	%
Alive with NED	28	56	14	28
Alive with disease	8	16	5	10
Died with disease	8	16	23	46
Died with unrelated causes	6	12	3	6
Lost follow up	0	0	5	10

23 patients (46%) in group II died with their disease. Six patients (12%) in group I and 3 patients (6%) in group II died of unrelated causes (Table 6).

At a median follow up period of 18 months for all patients, the 2-year actuarial overall survival (OS) was 67% and 55% with a median of 19 and 16 months in group I and II respectively. Although OS was higher in group I, the difference between both groups wasn't statistically significant ($P = 0.227$). Similarly, the 2-year disease free survival (DFS) was 72% and 60% with a median of 17 and 15 months in group I and II respectively, with no statistically significant difference between both groups ($P = 0.592$).

Discussion

Colorectal cancer is ranked as the fourth most frequently diagnosed cancer and second leading cause of cancer death in U.S., although mortality from CRC has been reduced during the past 30 years [9].

Local tumor control remains an important aim in the treatment of rectal cancer because of devastating morbidity and unsatisfactory treatment option for local recurrence [10].

Local failure rates after 5-year follow up after total mesorectal excision (TME) have decreased from about 28% to 10–15% Glimeliues *et al* [8], Sebag-Montefiore *et al* [3] reported that total mesorectal excision had been achieved in 93% of patients who underwent resection after preoperative radiotherapy with local failure rate at 5 years of 4.7% versus 11.5% in postoperative radiotherapy group, the overall negativity rate for circumferential resection margin was 89%, which compares favorably with the Dutch trial reported by Peeters *et al* [11] in which 77% of patients in the intention-to-treat analysis had tumor-free margins without tumor spillage.

Preoperative radiotherapy at biological effective doses above 30 Gy decreases the relative risk of a local failure by more than half (50%–70%). Postoperative radiotherapy decreases the risk by 30%–40% at doses that generally are higher than those used preoperatively. There are strong evidences that preoperative radiotherapy improves survival (by about 10%) [8].

This present study included 100 patients with resectable rectal cancer (T3–4, N0–2, M0). They were randomly assigned into two groups; group I (50 patients), who received preoperative radiotherapy & group II (50 patients) who received postoperative radiotherapy.

The median age of patients was 48 & 45 years in group I & II respectively. This age incidence is similar to that reported by Abou-Zeid *et al* [12] & Mohamed *et al* [13], where the median age was 46 years in their studies. However this median age is less than that reported in Western World studies. Gerard *et al* [14] reported a median age of 65 years. This age difference could be related to bad dietary habits with excess fat content in our country.

Bleeding per rectum was the most common presenting symptom; it was present in 86 % and 80 % of patients in group I and II respectively. Also, Mohamed *et al* (2005) found in their study that bleeding per rectum was the most common presenting symptom (83.5%). Distance of tumor from the anal verge ranged from 2–9 cm with a median of 5 cm which approximates that reported by Gerard *et al* [14]. They recorded a distance from the anal verge that ranged from 2–10 cm with a median of 6 cm in their study.

As regard the pathological types, adenocarcinoma was the most common type (48% & 54%), followed by Mucinous adenocarcinoma (34% & 38%), then signet ring carcinoma (18% & 8%) in group I and II respectively. This distribution approximates the figures found by Mohamed *et al* [13] who reported 64%, 31%, and 5% incidence of adenocarcinoma, Mucinous, and signet carcinoma respectively.

In this study, pretreatment CEA level was elevated in 8% & 16% of patients studied in group I and II respectively. Twelves *et al* [15] reported a lower incidence in their study (8.6%); however Giacchetti *et al* [16] reported a higher incidence rate (68%).

As far as clinical staging in group I is concerned, we found an incidence of stage II and III in 59% & 41% of patients respectively. Mohamed *et al* [13] reported a similar stage distribution in favor of stage II (40%). On the other hand, stage II and III tumors were found in 30% & 70% of patients in the series that was studied by Gerard *et al* [14].

Pathological staging in group I was in favor of earlier stages (6%, 16%, 38% and 40% for stages 0, I, II, and III respectively) while Elwanis *et al* [17] reported similar incidences of 6.9, 17, 37.9% and 38% for stages 0, I, II, and

III respectively after neoadjuvant chemoradiation with capecitabine.

Regarding pathological staging in group II, stage II incidence was 42% and stage III was 58% which is similar to some extent to that found in Gerard *et al*[14] series after preoperative chemoradiation with high dose radiotherapy and oxaliplatin-containing regimen.

In this study, abdomin-perineal resection was the most common surgical procedure and was done in 62% & 90% of patients in group I & II respectively. Low anterior resection was done in 15 (30%) & 5 (10%) of patients in group I & II respectively with a statistically significant difference (P = 0.011). Sauer *et al*[18] reported a double rate of sphincter sparing procedure in preoperative chemo-radiotherapy versus postoperative chemo-radiotherapy. Our figures differ from that reported by Gerard *et al*[19], where low anterior resection was the most common procedure (55%). The difference may be due to surgical decision that prefers to do abdomino-perineal resection for more oncologic safety regardless of down-staging after preoperative radiotherapy. Also age factor affects surgical decision, sphincter preservation in younger age (age group < 40 years was present in 32% & 26% of patients in group I and II respectively) was preferable.

Diverting colostomy was done in 8 out of 15 (53.3%) patients in group I who underwent sphincter sparing procedure. Also Gerard *et al*[19] recorded that a high percentage of diverting colostomy (72%) was done in preoperative radiotherapy arm, while Gerard *et al*[14] reported a percentage of 36%.

In this study, there was no early postoperative mortality. The most common postoperative morbidity was delayed wound healing (14%) which is similar to some extent to that reported by Camma *et al*(18%) [7].

Other less frequent postoperative morbidity was intestinal obstruction (6%) and anastomotic leakage (4%) which are comparable to that recorded by Read *et al*[20] (5.8% & 8.2%), and Camma *et al*[7] (5.2% & 5.2%) for intestinal obstruction and anastomotic leakage respectively. Also anastomotic stricture occurred in 4% of our patients which is similar to that reported by Frykholm *et al*[21] (2%) and there were no significant changes in late toxicity between preoperative and postoperative radiotherapy.

Local recurrence (LR) was the most common site of failure in this study. It was experienced by 10% & 32% of patients in group I and II respectively, the difference was statistically significant (P = 0.031). Distant recurrence was experienced by 12% & 20% of patients in group I and II respectively with no statistically significant difference (P = 0.083). Frykholm *et al*[21] compared preoperative with postoperative radiotherapy in resectable rectal cancer. Local recurrence was 13% vs. 22% in preoperative vs. postoperative radiotherapy respectively (P = 0.02).

At a median follow up of 18 months for all patients, the 2-year actuarial overall survival rate (OS) was 67% & 55% in group I & II respectively. Although OS was higher in group I but it didn't reach a statistically significant difference (P = 0.227). At a median follow-up of 24 months in group II, the 4-year actuarial OS was 39% while Sauer *et al*[18] reported a 5-year OS of 76% & 74% for preoperative vs. postoperative CRT respectively c (P = 0.08). Taher *et al*[22] reported a 10-year OS of 63% vs. 60% for postoperative chemotherapy vs. preoperative radiotherapy (P = 0.698).

In Swedish Rectal Cancer Trial (1997), 5-year OS was 58% vs. 48% for preoperative radiation therapy compared with surgery alone (P = 0.004). The difference may be due to the small sample size of our study.

In this study after a median follow-up of 18 months for all patients, the 2-year DFS was 72% & 38% in group I & II respectively without statistically significant difference (P = 0.592). At a median follow up of 24 months in group II, the 4-year DFS was 37%. Similarly Sauer *et al*[18] found no statistically significant difference in DFS with either preoperative or postoperative chemo-radiotherapy (P = 0.32). Taher *et al*[22] reported a 10-year DFS of 65% vs. 66% (P = 0.816) for postoperative chemo-radiotherapy vs. preoperative radiotherapy respectively.

Conflict of interest

The authors have no conflict of interest.

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Association between polycyclic aromatic hydrocarbons and human rectal tumor or liver cancer*

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Abstract ***Objective:*** The aim of this study was to investigate the effect of polycyclic aromatic hydrocarbons (PAHs) in rectal carcinoma and hepatocarcinoma genesis. ***Methods:*** The PAHs in the human rectal cancer and liver cancer tissues, the adjacent tissues and homologous tissues without rectal cancer or liver cancer were extracted by ultrasonic wave. The extracts were then cleaned up and enriched by solid phase extraction, analyzed by high performance liquid chromatography (HPLC) with fluorescence spectroscopy. ***Results:*** Four kinds of PAHs were detected in human rectal and hepatic tissues. The contents of pyrene, 2-methylanthracene and benzo (a) pyrene in both rectal cancer tissues and adjacent homologous tissues were higher than rectal tissues without rectal cancer, the differences were statistically significant ($P < 0.05$). The contents of phenanthrene in the three kind of tissue were not significant ($P > 0.05$). The differences of the content of each PAHs between rectal cancer and adjacent tissue were not significant ($P > 0.05$). The contents of the four PAHs in the three kinds of liver tissues were not statistically significant ($P > 0.05$). ***Conclusion:*** PAHs are found in human rectal tissues or hepatic tissues. The contents of PAHs in human rectal tissue may have an effect on the occurrence of human rectal cancer while the contents of PAHs in human hepatic tissues may have not ones.

Key words rectal cancer; liver cancer; polycyclic aromatic hydrocarbons (PAHs); high performance liquid chromatography (HPLC)

Although scholars have been explored extensively the pathogenic factors of rectal carcinoma and hepatocarcinoma genesis, etiology is not definite up to now. The morbidity and mortality of rectal carcinoma has increased year by year while the cute rate is not improved [1]. Polycyclic aromatic hydrocarbons (PAHs), is defined as two or more benzene rings arranging in the way of linear, angular or cluster-like. Carcinogenic, teratogenic and mutagenic are the prominent features of the PAHs [2]. PAHs are one of the first discovered persistent organic pollutants. Now the prevention of PAHs has caused widespread attention to the world [3]. PAHs can be directly absorbed though respiratory tract, digestive tract, skin etc or accumulated in animals and humans though food chain [4]. In theory, the human rectal tissues or hepatic tissues may contain PAHs. And presumably, the occurrence of rectal carcinoma and hepatocarcinoma may have association with PAHs in the cancer tissues.

This study was designed to detect the content of the PAHs in human rectal and hepatic tissues (cancer tissue and no cancer tissue) with the method of ultrasonic extraction, solid phase extraction and clean up-high performance liquid chromatography (HPLC) with fluorescence spectroscopy. Then we can confirm whether the PAHs exist in human rectal or hepatic tissues whether it's responsible with rectal cancer or liver cancer.

Materials and methods

Reagents and instruments

LC-240 HPLC (Perkin–Elmer company, USA); 250 mm × 4.6 mm i.d. reverse-phase C18 column (Aydac Company, USA); solid-phase enrichment column which packed by C18 (Tianjin Enrichment Technology Co., Ltd., China);

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DL-I solid-phase extraction device (Dalian Institute of Chemical Physics, Chinese Academy of Sciences, China); H66025 Ultrasonic Cleaning Machine (Wuxi Ultrasonic Electronic Equipment Factory, China); CM1900 frozen section machine (Leica Company, Germany); benzo (a) pyrene, pyrene, phenanthrene, 2-methylanthracene, fluoranthene, chrysene, 2-methylnaphthalene were spectroscopically pure reagent (Fluka company, USA); methanol, chromatographic pure reagent; n-hexane, acetone, methylene chloride, anhydrous sodium sulfate, naphthalene were analytical reagent.

The preparation of the eight kinds of PAHs' standard solution

Eight PAHs prepared with methanol as the solvent were used for the study: naphthalene: 50 μg/mL; 2-methylanthracene: 50 μg/mL; phenanthrene: 10 μg/mL; fluoranthene 5.0 μg/mL; pyrene: 5.0 μg/mL; 2-methylanthracene: 5.0 μg/mL; chrysene: 5.0 μg/mL; benzo (a) pyrene: 1.0 μg/mL. The standard solutions were frozen at -20 ℃ refrigerator for later use. They can be diluted to the appropriate concentration when used.

Specimens source and groups

Specimens were collected from the Department of Pathology, The Affiliated Hospital of Medical College Qingdao University, and confirmed by pathology. The rectal experiment was divided into three groups: the human rectal cancer tissue [20 cases, 9 males and 11 females, aged (51.1 ± 14.3) years], the adjacent tissue [20 cases, 9 males and 11 females, aged (51.1 ± 14.3) years], and rectal tissue without rectal cancer [5 cases, 2 males and 3 females, aged (43.3 ± 19.9) years].

The hepatic experiment was also divided into three groups: the human liver cancer tissue [15 cases, 9 males and 6 females, aged (55.4 ± 15.3) years], the adjacent tissue [5 cases, 3 males and 2 females, aged (45.1 ± 13.5) years]. There were no statistical significances in age, sex ratio among the above groups.

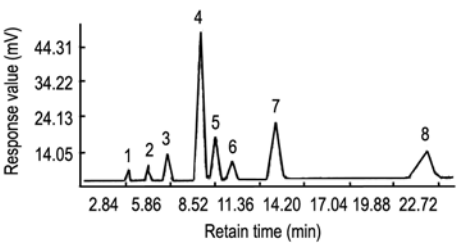

Fig. 1 Chromatogram of eight PAHs standard solution. 1: naphthalene; 2: dimethylnaphthalene; 3: phenanthrene; 4: fluoranthene; 5: pyrene; 6: 2-methyl anthracene; 7: chrysene; 8: benzo (a) pyrene

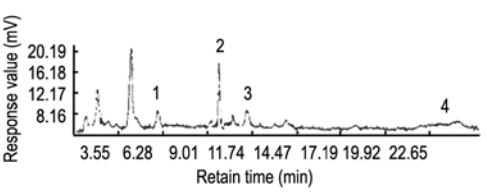

Fig. 2 Chromatogram of PAHs in rectal cancer. 1: phenanthrene; 2: pyrene; 3: 2-methyl-anthracene; 4: benzo (a) pyrene

Extraction and clean up of PAHs

Samples pre-treatment

The specimens were mashed into a paste. Assay sample (1.0 g) was inserted in a glass tube with 10 mL hexane - acetone (V:V = 1:1) and placed in an ultrasonic bath for 30 min. The solution was centrifuged for 5 min at 2500 rpm; the supernatant fluid was transferred into 10 mL glass tubes. Added hexane-acetone (V:V = 1:1) 10 mL into the tubes and repeated above steps. Subsequently the specimens were washed with three aliquots of hexane and the organic phase was collected, transferred into a 20 mL separating funnel with saturated sodium sulfate solution. After 1 min shaking and 1h placing, the supernatant fluid was aspirated to spare and concentrated to 2 mL in the fume hood.

Extraction and clean up

The C18 column was washed by methylene chloride, and then 5 mL methanol and 5 mL water passed. Before the column finishing, the concentration passed and the elate was abandoned. After 5 mL n-hexane-dichloromethane (V:V = 1:1) washing, the eluate was collected and evaporated down to yellow powder. Then 1 mL methanol was added and reconstituted to a final volume of 2 mL.

HPLC condition

The mobile phase was methanol-water (V:V = 80:20); the flow rate was 1.5 mL/min; injection volume was 20 μL; λ excitation was 407 nm and λ emission was 288 nm; the detection time was 1500 s; quantified by external standard; room temperature.

Statistical analysis

All values were expressed as mean ± standard error. PPMS 1.5 statistics software application data processing, variance analysis, significant level $\alpha = 0.05$.

Results

Chromatogram of eight kind of PAHs standard solution was presented in Fig. 1. Phenanthrene, pyrene, 2 - methyl-anthracene and benzo (a) pyrene were detected in all groups. Chromatogram of PAHs was presented in Fig. 2. Detection rate of PAHs in three rectal tissues were reported Table 1. Concentrations of PAHs in three rectal tissues were reported Table 2. From Tables 1 and 2, we could seen that the detection rate of pyrene and benzo

Table 1 Detection rates of PAHs in three rectal tissues [*n* (%)]

Groups	*n*	Phenanthrene	Pyrene	2-methylanthracene	Benzo (a) pyrene
Rectal cancer tissue group	20	18 (90)	20 (100)	17 (85)	20 (100)
Adjacent group	20	20 (100)	20 (100)	15 (75)	20 (100)
Non-cancer group	5	4 (80)	5 (100)	2 (40)	5 (100)

Table 2 Concentrations of PAHs in three rectal tissue (ng/g, $\bar{\chi} \pm s$)

Groups	Phenanthrene	Pyrene	2-methyl anthracene	Benzo (a) pyrene
Rectal cancer group	587.5 ± 121.3	907.1 ± 241.2	699.7 ± 185.7	1129.3 ± 333.9
Adjacent group	570.1 ± 103.3	820.8 ± 194.4	620.2 ± 137.8	998.3 ± 245.5
Non-cancer group	489.7 ± 96.6[a]	589.4 ± 107[b]	313.3 ± 98.6[b]	655.2 ± 105.4[b]

Comparison between groups: [a] $F = 1.27$, $Q = 0.6821–2.2533$, $P > 0.05$; [b] $F = 4.60–5.80$, rectal cancer group, adjacent group were compared with non-cancer group: $Q = 3.1018–4.7782$, $P < 0.05$, rectal cancer group compared with the adjacent group: $Q = 1.8291–2.0876$, $P > 0.05$

Table 3 Detection rates of PAHs in three liver tissues [*n* (%)]

Groups	*n*	Phenanthrene	Pyrene	2-methylanthracene	Benzo (a) pyrene
Liver cancer group	15	13 (87)	15 (100)	12 (80)	15 (100)
Adjacent group	15	15 (100)	15 (100)	10 (67)	15 (100)
Non-cancer group	5	4 (80)	5 (100)	3 (60)	5 (100)

Table 4 Concentrations of PAHs in three liver tissue (ng/g, $\bar{\chi} \pm s$)

Groups	Phenanthrene	Pyrene	2-methylanthracene	Benzo (a) pyrene
Liver cancer group	211.2 ± 111.3	277.1 ± 186.1	189.5 ± 114.4	378.4 ± 204.5
Adjacent group	167.4 ± 92.7	220.5 ± 154.9	150.6 ± 85.6	310.7 ± 160.4
Non-cancer group	144.2 ± 69.6	159.6 ± 117.8	103.4 ± 55.2	280.9 ± 108.7

Liver cancer group, adjacent group were compared with non-cancer group: F (0.83–2.11), Q (0.4633–2.7976), $P > 0.05$, liver cancer group compared with the adjacent group: Q (1.3247–1.7172), $P > 0.05$

(a) pyrene were all 100%, in rectal cancer tissues, adjacent cancer tissues, and non-cancer tissues. Philippine's detection rates were 90%, 100% and 80%. 2-methyl anthracite's detection rates were 85%, 75% and 40%. Content of phenanthrene was no significant difference ($P > 0.05$); pyrene, 2-methyl-anthracene and benzo (a) pyrene in rectal cancer tissues and adjacent tissues were higher than non-cancer tissues, the difference was statistically significant ($P < 0.05$); four PAHs was no significant differences in rectal cancer and adjacent tissues ($P > 0.05$). Detection rate of PAHs in three liver tissues were reported Table 3. Concentrations of PAHs in three liver tissues were reported Table 4. From Table 4, four PAHs was no significant difference in liver cancer, adjacent tissues and non-cancer tissues ($P > 0.05$).

Discussion

PAHs has a trace content in the environment, but epidemiological studies [4, 5] show that PAHs is endued with a magnified biological function and toxic effect as a result of biologically cumulative effect in food chain. In our previous studies [6, 7], we detect PAHs in human gastric cancer and lung cancer, and all the cancer tissues have a significantly higher content than the non-cancer ones. In this study, we prove that PAHs can be detected in human rectal cancer tissues and it might play an important role in the development and progression of human rectal cancer.

The results show that PAHs are not found with the incidence of liver cancer related, which may be due to hepatic degradation of PAHs dictates, from the papers [8, 9], PAHs are due to enzymatic hydrolysis of aromatic epoxides by liver microsomal cytochrome P450 (CYP450) enzymes in the CYP1A1, 1A2 and 1B1 oxidase enzyme such as monoaminoxidase, then turn under the action of hydrolytic enzymes into the cis, trans-glycol-type compounds, and further oxidize to dihydroxy epoxides by CYP enzyme. Then epoxides can be catalyzed by phase Ⅱ enzymes such as glutathione S-transferase enzymes and combine with glutathione covalent inactivation and detoxification, form into water-soluble sulfate and glucuronide and excrete through the urine and feces .

PAHs is thought to be activated by CYP4501A1, a member of CYP450 enzyme system, and then evolve into carcinogenic electrophilic epoxides after enter the body.

So the activity of CYP4501A1 isoenzyme becomes the key to decide the carcinogenicity of PAHs [8]. The activity of CYP4501A1 isoenzyme can be induced by PAHs, and the activity increases significantly in peoples with long-term exposure to PAHs [9]. Previous study indicates that people with high PAHs inductivity genotype have a higher risk of suffering from colorectal cancer and lung cancer than non-high-inductivity genotype [10, 11]. But no definite mechanisms of PAHs' carcinogenicity are founded in our study and farther experiments about this are needed.

By present, all the detections about PAHs are limited in environment, food, animals and plants, and few researches about the human body tissues can be founded. In this study, we prove that PAHs exist in human rectal and liver tissues with the methods of ultrasonic extraction, solid phase extraction and HPLC. Further analysis shows that PAHs content are higher in rectal cancer tissues than non cancer ones, and there is a significant difference between each other ($P < 0.05$). This indicates that PAHs may be associated with the occurrence of rectal cancer and it may be one of the most important reasons to generate human rectal cancer. Therefore, controlling PAHs contamination and reducing PAHs exposure have an important meaning for cancer prevention.

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Radiobiological effect of abdominal X-ray hypo-fraction irradiation on Wistar rats liver

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Abstract ***Objective:*** The aim of our study was to investigate the impact of abdominal hypo-fraction irradiation on liver damage in rats so as to provide a reference for its clinical application. ***Methods:*** A total of 100 Wistar rats were equally randomized to five groups as control, 4 Gy, 6 Gy, 8 Gy and 12 Gy group, and the corresponding fractionated doses were offered. Liver functions were examined at the 2nd, 4th, 6th, 8th and 10th week after irradiation. Morphological changes were observed by HE staining. Expressions of Bcl-2 and Bax were examined by immunohistochemical technique. ***Results:*** In all irradiation groups, hepatocellular swell, degeneration, necrosis and even hepatic fibrosis could be seen. The differences of the liver coefficient, Glutamyl pyruvic transaminase (GPT), Glutamyl oxaloacetic transaminase (GOT) were significant among the groups and different time points (F = 11.833–781.972, F = 20.857–264.692, P < 0.001). Expressions of Bcl-2 and Bax were significantly different between each group (F = 211.607, 116.577; P < 0. 001), and between each time point (F = 54.083, 68.749; P < 0. 001). ***Conclusion:*** Compare with conventional fraction, abdominal hypo-fraction irradiation may cause radiation damage to rat liver, being dose-and-time dependent. Up-regulation of activating apoptosis protein Bax and down-regulation of inhibiting apoptosis protein Bcl-2 may involve in the process.

Key words radiotherapy; dose fractionation; liver; radiobiological effects; apoptosis; Bcl-2/Bax

The liver is an important metabolic organ, and the studies of liver radiobiology were quite a lot. The liver belongs to late effective normal tissues, but previous related studies mostly concentrated on late side effects of the liver after the conventional fractionated radiotherapy. Therefore we designed to study the liver early response in the abdominal hypo-fraction irradiation. To provide the basic parameters for the clinical application of abdominal hypo-fraction radiotherapy, we study early changes in biochemical indicators and pathological features of radioactive liver injury through the abdomen hypo-fraction irradiation in rats.

Materials and methods

Experimental animals and grouping

A total of 100 SPF Wistar rats (4–5 weeks old) were chose, male and female each half. Its body weight ranged from 200 to 250 g and purchased from the Qingdao Municipal Institute for Drug Control. In natural light, we gave an adequate standard feed and water, then kept rats at room temperature of 16–20℃. The rats were randomly divided into control group, the 4 Gy group, 6 Gy group, 8 Gy group and 12 Gy group (n = 20).

Irradiation methods

The rats were anesthetized by intra-peritoneal injection with volume fraction of 10% chloral hydrate (350 mg/kg). Then the rats were fixed at the flat panel supine. Next, we placed the fixed rats in the simulator and outlined the radiation field: the upper bound for the costal arch edge, the lower bound for the upper edge of the iliac crest. We marked the radiation field of 4 cm × 2 cm on the surface of the body, and the remaining parts were blocked with the MLC. We located the satisfying rats under a Varian 23EX linear accelerator with 6MV X-ray irradiation. Each group exposed to the planned irradiative dose fractionation. Source-to-skin distance was set to 100 cm in another plus 1 cm organization compensation, and X-ray dose rate was 300 cGy/min.

Testing indicators and methods

Morphological observation

Four rats were selected from each group randomly after irradiation at the end of the 2nd, 4th, 6th, 8th and 10th weeks. We weighed rats body and dissected its fresh liver tissue, then calculated the liver coefficient (organ coeffi-

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cient = [(Organ mass weight / Body weight) × 100%]. We put the liver tissues into 4% neutral buffered formalin fixed, conventional dehydration, transparent, embedded in paraffin sections. We observed morphological changes under the microscope by hematoxylin-eosin (HE) staining.

Detection of GPT and GOT

We selected four rats from each group randomly after irradiation at the end of the 2nd, 4th, 6th, 8th and 10th weeks. Rats were killed by cervical dislocation, then we exsanguinated 5 mL from the abdominal aorta, and leaving the liver tissue. We measured GPT and GOT in arterial blood centrifugation serum by automatic biochemical analyzer.

Bcl-2 and Bax detection

According to the kit instruction, Bcl-2 and Bax expression detected strictly by immunohistochemical method, using PBS buffer as negative control instead of primary antibody. We randomly selected five fields of vision from each slice under a microscope (400 times), counting 200 cells per field of vision, and calculated the percentage of positive cells.

Statistical analysis

We carried out data processing by the application of the SPSS 13.0 and PPMS 1.5 [1] statistical software. Data was analyzed by using factorial design analysis of variance ($P < 0.05$ for the difference was significant).

Results

Changes in liver morphology

Under microscopy the hepatic lobule of the control group showed a clear structure and rows of hepatic cords. But the rat liver in exposed group were observed in varying degrees of liver cell swelling, degeneration, necrosis, and even fibrosis. Injury of the 12 Gy group was significantly higher than the 4 Gy group.

Statistical analysis of liver coefficient, serum GPT, GOT

Compared among the groups, the results of the liver coefficient, the GPT, GOT in the blood showed significant differences (the $F = 11.833–781.972$, $P < 0.001$). Differences were significant at different times in the same group ($F = 20.857–264.692$, $P < 0.001$; Tables 1–3).

Comparison of Bcl-2 and Bax expression

The cytoplasm of Bcl-2 positive cells showed uniform diffuse claybank. Bcl-2 protein expression levels of the irradiated groups were declining. In the 12 Gy group Bcl-2 expression was weakly positive to negative. The differences of Bcl-2 expression were significant in each group, but also significant at different time points ($F = 211.607$, 54.083, $P < 0.001$; Table 4).

Bax positive cells mainly showed that the cytoplasm and some nuclei were stained yellow or claybank. The control group only had a small amount of Bcl-2 protein expression, but all irradiated groups had a considerable number of positive cells. Among them, the rats liver in 12 Gy group and 8 Gy group had strong Bcl-2 protein expression and were stained to claybank. Compared between the groups, the results of Bax expression showed significant differences ($F = 116.577$, $P < 0.001$). In the same group differences were significant among to the liver dissected at different time points ($F = 68.749$, $P < 0.001$; Table 5).

Discussion

Along with clinical application of SRT, 3D-CRT, IMRT, IGRT, proton therapy, fast neutron therapy, hypofraction irradiation therapy is increasingly outstanding. Through the increase of fractionated dose, hypo-fraction irradiation therapy can kill cancer cells and hypoxic cells as much as possible to reduce tumor cell repopulation and improve local tumor control rate [2, 3]. However the incidence of normal tissue complications, especially the tolerance of late response tissues is a restrictively factor to improve tumor radiotherapy therapeutic ratio (TR) [4]. In the radiotherapy of abdominal tumors such as gastrointestinal, liver and gallbladder, the liver is an important involving organ of dose-limiting, and its tolerability of radiotherapy, is a valuable discussion of radiobiology [5]. Recent experience from a Canadian study [6] highlights the feasibility, safety, and efficacy of this strategy: 31 patients with HCC, Child-Pugh class A, were treated with highly conformal RT, and the 9-month in-field local control rate was 78%, with a median survival of 11.0 months. Mateen studied the feasibility of concomitant chemoradiation using gemcitabine in primary liver cancer, and confirmed that concomitant gemcitabine and ERT is a feasible option with moderate toxicity in advanced HCC [7].

At present we search for the study of the problem, especially in basic experimental research rarely. In this study, the Wistar rats received abdominal X-ray hypo-fraction irradiation in accordance with the planned fractionated doses. We observed the changes of the liver morphology, function and apoptotic protein expression of Bcl-2 and Bax, to investigate the early radiobiological effects of rats liver and its possible mechanism.

We found morphological changes of the experiment samples: (1) With naked eyes, rat liver surface and the cut surface shows different extent of dark red. The higher the fractionated dose, the more obvious these changes; (1) under the microscope, pathological sections of 6 Gy, 8 Gy and 12 Gy group see the expansive veins and sinusoidal congestion, hepatic venous occlusive disease (VOD),

Table 1 Comparison of liver coefficient (χ/%, $\bar{\chi} \pm s$)

Groups	2nd week	4th week	6th week	8th week	10th week
Control	1.31 ± 0.20	1.40 ± 0.28	1.26 ± 0.14	1.32 ± 0.16	1.27 ± 0.10
4 Gy	1.27 ± 0.47	1.26 ± 0.14	1.19 ± 0.07	1.09 ± 0.11	1.05 ± 0.03
6 Gy	1.28 ± 0.11	1.25 ± 0.07	1.25 ± 0.13	1.09 ± 0.02	1.04 ± 0.05
8 Gy	1.35 ± 0.52	1.29 ± 0.17	1.13 ± 0.06	1.00 ± 0.07	0.94 ± 0.05
12 Gy	1.32 ± 0.09	1.26 ± 0.14	1.15 ± 1.00	0.96 ± 0.03	0.85 ± 0.06

Liver coefficient between groups at the same time point, $F = 11.833$, $P < 0.001$; Liver coefficient within the group at different time points, $F = 28.822$, $P < 0.001$

Table 2 Comparison of GPT (c/μmol·L^{-1}, $\bar{\chi} \pm s$)

Groups	2nd week	4th week	6th week	8th week	10th week
Control	55.63 ± 4.16	57.60 ± 3.49	57.00 ± 4.20	56.77 ± 1.07	56.65 ± 3.13
4 Gy	55.20 ± 2.77	59.00 ± 1.00	61.45 ± 6.00	63.40 ± 3.29	64.60 ± 8.46
6 Gy	63.40 ± 3.64	66.80 ± 4.49	70.40 ± 4.39	72.40 ± 5.85	76.40 ± 5.68
8 Gy	69.00 ± 3.65	72.80 ± 8.22	76.00 ± 6.89	77.20 ± 5.06	79.80 ± 5.40
12 Gy	65.00 ± 2.55	71.20 ± 1.92	83.20 ± 5.31	86.00 ± 4.49	97.00 ± 4.30

GPT between groups, $F = 77.636$, $P < 0.001$; GPT at different time points, $F = 20.857$, $P < 0.001$

Table 3 Comparison of GOT (c/μmol·L^{-1}, $\bar{\chi} \pm s$)

Groups	2nd week	4th week	6th week	8th week	10th week
Control	6. 64 ± 0.39	6. 18 ± 0.23	6. 31 ± 0.47	6. 52 ± 0.53	6. 32 ± 0.44
4 Gy	8. 64 ± 0.91	9. 71 ± 0.42	10.62± 0.48	12.04 ± 0.29	13.01 ± 0.97
6 Gy	9. 50 ± 0.60	10.31 ± 0.76	11.34 ± 0.42	13.14 ± 0.17	14.42 ± 1.28
8 Gy	9. 85 ± 0.47	12.12 ± 0.33	13.48 ± 0.76	15.06 ± 0.40	17.39 ± 1.05
12 Gy	10.42 ± 0.61	14.46 ± 0.49	16.42 ± 0.48	18.33 ± 0.50	20.91 ± 1.04

GOT between groups, $F = 781.972$, $P < 0.001$; GOT at different time points, $F = 264.692$, $P < 0.001$

Table 4 Comparison of Bcl-2 protein expression (χ/%, $\bar{\chi} \pm s$)

Groups	2nd week	4th week	6th week	8th week	10th week
Control	35.40 ± 4.16	34.60 ± 2.79	34.40 ± 4.15	36.40 ± 1.14	35.40 ± 2.60
4 Gy	32.00 ± 2.23	26.89 ± 2.05	24.60 ± 2.07	20.60 ± 2.40	19.40 ± 2.70
6 Gy	28.60 ± 2.07	24.40 ± 2.41	21.60 ± 2.80	20.60 ± 1.12	17.60 ± 2.07
8 Gy	24.00 ± 2.55	23.60 ± 1.82	21.80 ± 1.30	17.40 ± 1.81	15.20 ± 1.30
12 Gy	22.80 ± 2.39	21.60 ± 1.51	17.00 ± 1.87	14.00 ± 2.00	12.00 ± 1.58

The differences of Bcl-2 expression were significant between groups ($F = 211.607$, $P < 0.001$); The differences of Bcl-2 expression were significant in each group ($F = 54.083$, $P < 0.001$)

Table 5 Comparison of Bax protein expression (χ/%, $\bar{\chi} \pm s$)

Groups	2nd week	4th week	6th week	8th week	10th week
Control	12.80 ± 1.64	13.60 ± 1.14	13.40 ± 2.07	13.40 ± 1.67	14. 0 ± 1.87
4 Gy	14.20 ± 1.30	16.60 ± 1.81	20.40 ± 1.94	21. 2 ± 1. 92	24.40 ± 2.51
6 Gy	14.80 ± 3.19	16.00 ± 2.64	21.00 ± 1.50	24.00 ± 1.58	25.00 ± 1.58
8 Gy	19.80 ± 1.64	20.00 ± 2.00	22.00 ± 1.58	25.60 ± 3.04	29.80 ± 2.77
12 Gy	19.40 ± 1.14	22.60 ± 2.41	24.80 ± 2.59	27.60 ± 2.07	30.20 ± 1.92

The differences of Bax expression were significant between groups ($F = 116.577$, $P < 0.001$); The differences of Bax expression were significant in each group ($F = 68.749$, $P < 0.001$)

Spotty necrosis, necrosis, the increase of collagen fibers at portal area and around the central vein. Among the exposed groups, morphological changes appeared in the 12 Gy group first. It indicated that the liver morphological injuries were aggravated with the increase of fractionated doses in the same equivalent total dose. In the same group, liver morphological change was progressively increased with the increase of total exposure. It caused by the increase of collagen fibers after liver cell necrosis. The experimental results is consistent with the four stages

summary of the pathological development of radioactive liver injury [8]. The statistics show that the damage of the liver lobule after irradiation Presents a dose-and-time dependent curve. The fatal injury of a large number of liver cells necrosis is irreversible, leading the development of liver injury to the direction of radioactive liver fibrosis.

GPT, GOT are specific serological markers to reflect impaired liver function. Impaired liver function because of liver cell inflammation and necrosis will lead to the GPT and GOT significantly higher, and GOT change is more significant. We considered that GPT is found primarily in non-mitochondrial of the liver cells, 80% of GOT present in the mitochondria of liver cells. Larger radiation damage to the mitochondria resulted in the release of mitochondrial GOT [9]. In this study changes in liver function is consistent with changes in liver morphology. This indicates that a single large-dose caused liver tissue to reduce the radiation tolerance.

Bcl-2 gene family is one of the major regulatory genes of apoptosis in mammalian cells, playing an important role in the X-ray-induced apoptosis process. The ratio of anti-apoptotic and pro-apoptotic protein in Bcl-2 family is the key to determine the cells sensitivity to death sign [10]. Bcl-2 is one of the strongest anti-apoptotic effects ever found. Bax is also one of the members of the family, but its role is to induce apoptosis. Therefore, Bcl-2/bax whom displays the ratio of the pro-apoptotic and anti-apoptotic forces determine the sensitivity of cells to apoptotic stimuli. Many studies have shown that Bcl-2/Bax involved in irradiative damage to normal cells and was significantly related to cell apoptosis [11]. Our results show that hypofraction irradiation can up-regulate expression of Bax and down-regulate expression of bcl-2 in Wistar rat liver. The decrease of bcl-2/bax ratio suggested that hepatocyte apoptosis may be related to bcl-2/bax.

In summary, the liver tissue damage caused by the irradiation may be related to highly expressed apoptotic protein Bax and low expression of apoptosis protein Bcl-2. The severity of their damage shows a dose-and-time dependent curve. Regarding to the reduced radiation tolerance of liver tissue caused by increasing the single split dose, we should try to improve the accuracy of radiotherapy to reduce the exposure of normal liver tissue. We need pay special attention to the protection of the liver tissue especially in hypo-fraction radiotherapy.

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Comparative analysis of therapeutic efficacy of ^{131}I in different clinical stages postoperative patients with papillary thyroid carcinoma

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Abstract ***Objective:*** The aim of this study was to compare the effect of ^{131}I therapy of different clinical stages in postoperative patients with papillary thyroid carcinoma (PTC). ***Methods:*** Eighty-seven PTC patients after surgery ablated with high doses of ^{131}I from 2004 to 2010 were retrospectively reviewed. The efficacy of ^{131}I therapy was assessed by three diagnostics that serum thyroglobulin (Tg) was normal or significantly reduced, ^{131}I whole body scan (^{131}I-WBS) was negative or the metastases shrank or the number of them decreased and new metastases was not found in cervical ultrasound examination. The χ^2 test was used to analyze 3 factors which might affect the therapeutic efficacy of ^{131}I in patients of different clinical period, including different surgical ways (total or subtotal thyroidectomy along with half or double sides neck lymph node dissection), age (< 45 years and ≥ 45 years) and ablative ^{131}I dose. ***Results:*** Of 87 patients, the effective rate of 46 patients I stage was 89.13% (41); the effective rate of 22 cases III stage was 77.27% (17); the effective rate of 19 cases IV stage was 36.84% (7). The corresponding intra-groups statistical difference of 3 stages was significant by χ^2 test (χ^2 = 1.72, 19.03, 6.87; $P > 0.25$, $P < 0.005$, $P < 0.01$). The effective rate was 91.67% (44) in 48 cases undergoing total thyroidectomy; the effective rate was 53.85% (21) in 39 patients undergoing subtotal thyroidectomy. There was a significant difference between the two groups above by χ^2 test (χ^2 = 16.291; $P < 0.005$). ***Conclusion:*** The efficacy of ^{131}I ablation of stage I and stage III in postoperative PTC patients was almost alike, while the efficacy of stage IV descended markedly. The results was mainly determined by residual thyroid tissue size because of different surgical modus.

Key words thyroid carcinoma; surgery; operative; iodine radioisotopes; radionuclide imaging

Thyroid cancer rate appears to be rising distinctly year by year. Differentiated thyroid carcinoma (DTC) is the most common type, accounting for 89% [1, 2] of thyroid malignancy, in which papillary thyroid carcinoma (PTC) is the most frequent endocrine cancer. Therefore, people pay more attention to the treatment and prognosis of postoperative patients with PTC. Currently, it is general acknowledged that the radioiodine (^{131}I) treatment is used to remove postoperative residual thyroid tissues and metastasis and recurrence. In 2002, Union International Control Cancer (UICC) published the latest edition of clinical stages. It is very necessary to understand if they are different about the effect of ^{131}I therapy of different clinical stages in postoperative PTC patients. 87 cases who had undergone high doses of ^{131}I therapy were retrospectively reviewed from 2004 to 2011 in our hospital. The aim of this study was to compare the effect of ^{131}I therapy of different clinical stages in postoperative PTC patients.

Patients and methods

Patients

Eighty-seven PTC patients (21 males, 66 females; age rang: 6–74 years; mean age: 40 years) were proved pathologically after removing primary tumor and undergoing total or subtotal thyroidectomy along with neck lymph node. Forty-eight cases had undergone total thyroidectomy, and 39 cases subtotal thyroidectomy. It was 1–24 months from postoperative to the first ^{131}I remnant ablation therapy, average 4 months. They were followed up for 2–4 years, including 2 dead cases. One case of III stage died of pancreatic cancer and 1 case of IV died of unknown causes.

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Clinical stage and ablative ^{131}I dose

According to the Sixth Edition (latest edition) TNM stage recommendations of the 2002 UICC and the operation records and pathological results, 87 patients were classified to different clinical stages, 46 cases belong to I stage, 0 case II, 22 cases III, 19 cases IV. Forty-one cases of I stage were effective and their mean therapeutic dose was 8.14 GBq (rang 3.7–18.5 GBq). Seventeen cases of III stage and 7 cases of IV stage were effective and their mean therapeutic doses were 6.56 GBq (range 3.7–14.8 GBq), and 13.32 GBq (7.4–18.5 GBq), respectively.

Methods of radioiodine therapy

Before ^{131}I therapy, all the patients were required to withdraw thyroxine for at least 4–6 weeks, take a no-iodine diet, and stop using any drug with iodine. Some routine examinations including blood routine test, renal function, hepatic function, cervical ultrasound, serum FT_3, FT_4, TSH, TG and TgAb were performed. According to the guidelines for thyroid cancer of ^{131}I ablation in the American Thyroid Association 2009, the first ^{131}I ablative doses range of remnant thyroid tissue was 2.96–3.7 GBq (6 years for 2.59 GBq). The doses of ^{131}I were given 3.7–7.4 GBq for eliminating lymph node metastases. The mean therapeutic times of all cases was 2.3 times (range 1–5 times). All the patients were observed for 5–7 days after ^{131}I therapy and then underwent ^{131}I whole body scan (^{131}I-WBS) to estimate the ^{131}I uptake of the remnant thyroid and metastases. If there were metastases, the patients would be considered to reuse ^{131}I therapy after 3–6 months.

Assessment of therapeutic results

Negative serum Tg and ^{131}I-WBS were marked as cured; negative serum Tg and shrink of focus or reduction of the number of metastases in ^{131}I-WBS were looked as improved; serum Tg reduction and no changing of the size or the number of metastases in ^{131}I-WBS and no finding new metastases in neck ultrasound were indicated stable; higher blood Tg, appearance of new metastases or the size increase of original metastases or the death were considered as treatment failure.

Statistical analysis

This retrospective study was analyzed by χ^2 test.

Results

Therapeutic efficacy of ^{131}I in different clinical stages

The intra-stages statistical difference of 3 stages above was significant by χ^2 test (χ^2 = 19.558, P < 0.005). The total effective rate of I stag was 89.13% and it was higher than that of III and IV stages. The therapeutic efficacy of ^{131}I was no significant difference between I stages and III stages (χ^2 = 1.72, P > 0.25, while there was significant difference between I and IV, III and IV (χ^2 = 19.03, 6.87, P < 0.005, P < 0.01; Table 1).

Table 1 Therapeutic efficacy of ^{131}I in different clinical stages (*n*)

Stages	Effect			Failure	Effect rate (%)
	Cured	Improved	Stable		
I	22	11	8	5	89.13
III	5	10	2	5	77.27
IV	0	2	5	12	36.84
Total	27	23	15	22	

Table 2 Therapeutic efficacy of ^{131}I in surgical ways and age (*n*)

Surgery modus and age	*n*	Effect	Failure	Effect rate (%)
Surgery modus				
Total thyroidectomy (TT)	48	44	4	91.67
Simple TT	12	12	0	
TT + half side neck lymph node	24	24	0	
TT + double sides neck lymph node	12	8	4	
Subtotal thyroidectomy (STT)	39	21	18	53.81
Simple STT	17	11	6	
STT +half side neck lymph node	15	8	7	
STT+half sides neck lymph node	7	2	5	
Age (years)				
< 45	38	33	5	86.84
≥ 45	49	32	17	65.31

Therapeutic efficacy of ^{131}I and surgical ways

The effective rate was 91.67% in 48 patients undergoing total thyroidectomy. It was higher than the effective rate of the 39 cases undergoing subtotal thyroidectomy. There was statistically significant difference in surgical ways between the 2 groups above (χ^2 = 16.291, P < 0.005; Table 2).

Therapeutic efficacy of ^{131}I and different age

In 38 patients of < 45 years, the effective rate was 86.84%. In 49 patients of ≥ 45 years, the effective rate was 65.31%. There was statistically significant difference in age between the 2 groups (χ^2 = 5.254, P < 0.05; Table 2).

Discussion

PTC was characterized with distinctive features of multi-centricity [3–5]. 38%–87% of PTC patients were found microscopic lesions in the contralateral lobe [6, 7]. There are still 40%–45% [8] residual lesions after operation. It has been reported in the literature that 80%–87% DTC still remain normal thyroid ^{131}I uptake function [9]. Local and distant metastases were also commonly found in some patients before surgery, and most of the metastasis could uptake ^{131}I. Therefore, ^{131}I can effectively elimi-

nate thyroid remnant and postoperative metastasis.

According to the Sixth Edition (latest edition) TNM stage recommendations of the 2002 UICC [10], PTC is divided into four stages. The therapeutic effect of ^{131}I varies. The results of this study show ^{131}I treatment effect is similar in I and III patients. While the curative effect of IV PTC patients was significantly lower than that of I stage and III stage. This suggests that it should be different for stage IV patients in ^{131}I treatment method, ^{131}I dose and treatment cycle time. It may be appropriate to increase the dose of ^{131}I therapy and shorten interval time. Because PTC patients develop easily lymph node metastasis in early stage, II cases of ≥ 45 years are less. PTC patients of < 45 years have been diagnosed and treated before the occurrence of distant metastases with enhancement of their health awareness, which is the reason of lack of II stage patients. It was also reported that II stage PTC patients had the best therapeutic efficacy of ^{131}I [11] and their age and pathological types did not affect the results. Although there was no II stage in the 87 PTC patients, II stage was involved in the result of I stage and III stage. So we believe the result is in concordance with the literature above.

There are different lesion sizes, encroachment outside thyroid and lymph node metastasis or distant metastasis in different clinical stages, so their surgical ways are different. The therapeutic efficacy of ^{131}I of the total thyroidectomy is superior to the efficacy of the subtotal resection ($P < 0.005$). In this study, the results show that the volume of residual thyroid tissues is crucial in ^{131}I therapy. As PTC patients of stages I and III have no or light encroachment outside thyroid and lymph node metastasis is limited, the number of total thyroidectomy patients is larger and the therapeutic efficacy of ^{131}I is better. While IV stage patients could not undergo total thyroidectomy with distinct infiltration to surrounding tissue, vascular encroachment and lymph node metastasis or distant transfer. Therefore, it increased distantly the difficulty of ^{131}I treatment in post-operation patients. This was an important reason that the therapeutic efficacy of ^{131}I of stage IV was significantly lower than that of stage I and III. We believe that the difference of the efficacy of ^{131}I in different clinical stages distantly correlates with operation approach. Thus, surgeons would be proposed to refer to the related reference guide to enforce surgery for PTC patients [12, 13] (such as the diagnosis and treatment guidelines of American Thyroid Association Thyroid nodules and DTC) and resect thyroid tissue as much as possible under the premise of no damaging to the parathyroid glands tissue. This can improve the therapeutic efficacy of ^{131}I.

It has been reported that the treatment effect in PTC patients of < 45 years is better than that of ≥ 45 years old patients [11]. Some scholars also believed that age did not affect the therapeutic efficacy of high-dose ^{131}I treatment [14]. In this study, the therapeutic efficacy of < 45 years old patients was good, mainly because they were all in I stage. Their total removal rate was high and residual focus was small and the treatment efficacy increased obviously. So we believe that age is not the primal influence factor in the therapeutic efficacy of ^{131}I treatment. In 87 cases, a 37 years old PTC patient of stage I was performed the total resection, but she began to use ^{131}I treatment after 24 months. Although she used 5 times, she still developed pulmonary metastases and delayed efficacy. It is evident that the first ^{131}I ablative time can also affect ^{131}I ablative efficacy. So we propose that PTC patients, whose focus diameter is > 4 cm or < 4 cm along with external thyroid invasion or distant metastases, should use ^{131}I treatment after operation as early as possible. This can enhance ^{131}I treatment efficacy in some extent.

It is worth to discuss how ^{131}I ablative dose affects the treatment effect. Some scholars have suggested that high-dose ^{131}I was used for several times to improve the efficacy [15, 16], but in this study the mean total dose of ^{131}I thyroid remnant and metastases were 8.14 GBq and 6.56 GBq in the effective patients of stage I and III. There was a better efficacy that the PTC patients were used 3.7–5.5 GBq after ^{131}I thyroid remnant. The view is concordance with the other study [17]. The therapeutic mean dose of IV patients is 13.32 GBq due to big residual thyroid tissue and distant metastases. It was higher than that of I stage and III stage, but the therapeutic efficacy of stage IV was not been changed. That is to say that ^{131}I ablative dose is not a main factor to affect ^{131}I curative effect, but we may adjust adequately the dose of ^{131}I to achieve the purpose of therapy according to the different feature of PTC patients.

By comparison the therapeutic efficacy of ^{131}I in different clinical stage, the nuclear medicine workers must read carefully the operation records and consider firstly residual thyroid tissue size to make a treatment plan for patients. Thus blind treatment will be avoided.

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Clinical outcome analysis of 98 elderly women with early-stage breast cancer undergoing modified radical mastectomy or simple mastectomy

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Abstract ***Objective:*** The aim of our study was to analyze the clinical results and prognosis for early elderly patients after surgery and to explore the rational treatment. ***Methods:*** Between January 1992 and December 2008, 98 early elderly breast cancer patients aged ≥ 65 years were treated with surgery, of which 52 patients received modified radical mastectomy and 46 patients received simple mastectomy. ***Results:*** Sixty-four (65.3%) patients had comorbidities including coronary heart disease, hypertension, diabetes, etc. After a median follow up of 56 months (21 to 280 months), the 5-year cumulative survival rate of breast modified radical mastectomy group and mastectomy group were 84.0% and 82.7%, separately (P = 0.653). The 5-year recurrence rate were 3.8% and 8.1%, separately (P = 0.504). ***Conclusion:*** The simple mastectomy is suitable for the treatment of early elderly breast cancer patients for its lower complication and recurrence rate. Early old women with breast cancer may be safely treated by simple mastectomy. Our findings suggest that modified radical mastectomy does not significantly increase the overall survival.

Key words elderly women; modified radical mastectomy; mastectomy

Breast cancer is the most common malignant tumor in women, as the second leading cause of cancer-related death in the world. In an aging population an increasing number of breast cancers is diagnosed in elderly women. In western countries, about 43% of the newly diagnosed breast cancer patients are aged more than 65 years [1, 2]. Hence, breast cancer has been severely threatening the health and life of elderly women. In 2008, more than 15% of patients with breast cancer in China were aged 65 years or older at the time of diagnosis [3]. It is remarkable that the tumor biology, physiological and psychological features appear to be different in elderly patients with breast cancer than in younger ones, and until now, there is no adherence guideline improving breast cancer cure and care in the elderly in the same way as expected in younger population [4]. Therefore, it is important to recognize above mentioned facts, and eventually guide elderly patients with breast cancer toward the most appropriate treatment strategies.

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Patients and methods

General data

Between January 1992 and December 2008, 98 women with breast cancer (stages I–II) were treated with surgery in our hospital (Department of Oncological Surgery, The Affiliated Hospital of Logistics College of Chinese People's Armed Police Force, Tianjin, China). Their ages ranged from 65 to 89 years (median, 71 years). The patients all had pathologically confirmed, 64 cases (65.3%) combined with cardiac-cerebral vascular disease, diabetes and chronic respiratory disease; 20 cases (20.4%) combined with two more diseases. Breast cancer was defined according to WHO Histological Classification of Breast Cancer (2003), the six edition of the tumour node metastasis (TNM) classification from AJCC. The clinical and pathological features were shown on Table 1.

Surgical methods

Fifty-two patients received modified radical mastectomy, among them, 15 cases with preservation of the pectoralis major muscle, 37 cases with preservation of both the pectoralis major and minor muscles, axillary dissection consisted of removal of the lymph nodes at level II

Table 1 The clinical and pathological features of 98 elderly breast cancer patients

Clinical features	*n* (%)	Modified radical mastectomy group	Mastectomy group	*P*
Age (years)				> 0.05
65–69	40 (40.8)	23	17	
70–79	47 (48.0)	25	22	
80–89	11 (11.2)	4	7	
TNM stage				> 0.05
I	28 (28.6)	11	17	
II	70 (71.4)	41	29	
Histologic type				> 0.05
Infiltrating ductal carcinoma	64 (65.3)	37	27	
Intraductal papillary carcinoma	10 (10.2)	4	6	
Adenocarcinoma	12 (12.2)	7	5	
Other carcinoma	12 (12.2)	5	7	
Histological grade				> 0.05
I + II	50 (86.2)	24	26	
III	8 (13.8)	6	2	
Indeterminate	40	22	18	
Estrogen receptor				> 0.05
+	66 (81.5)	36	30	
–	15 (18.5)	10	5	
Indeterminate	17	6	11	
Progesterone receptor				> 0.05
Positive	55 (69.6)	30	25	
Negative	24 (30.4)	15	9	
Indeterminate	19	6	13	
Her-2				> 0.05
Positive	9 (13.0)	4	5	
Negative	60 (87.0)	31	19	
Indeterminate	29	11	18	
No. of positive axillary lymph nodes				
0	43 (82.7)			
1–3	8 (15.4)			
≥ 4	1 (1.9)			

and III. Simple mastectomy was performed in 46 cases.

Postoperative adjuvant chemotherapy

Thirty-three (33.6%) patients received adjuvant chemotherapy includes cyclophosphamide/methotrexate/5-fluorouracil (CMF), cyclophosphamide/doxorubicin/5-Fluorouracil (CAF) or cyclophosphamide/Epirubicin/5-Fluorouracil (CEF) regimen. Twenty-four (24.4%) patients received radiotherapy after operation or radiotherapy, 41 (41.8%) patients were treated with Tamoxifen or aromatase inhibitors (oral route) for 5 years.

Statistical analysis

SPSS 13.0 statistical analysis software was used. Differences in characteristics and adherence to guidelines between the two age groups were analyzed by means of Pearson's χ^2 test. Curves for overall survival were estimated by the Kaplan-Meier method and compared using the Log-rank test. $P < 0.05$ was regarded as statistically significant difference.

Results

Ninety-eight patients were begun to follow-up after operation, with a median duration of follow up of 56 months (21–280 months). Two patients who received modified radical mastectomy had bone metastasis (after 23 months) and lung metastasis (after 24 months), respectively. One patient developed a local relapse 25 months after mastectomy, and then treated with local excision and endocrine therapy. There are 3 patients deaths from breast cancer, 2 patients deaths from cranial vascular disease, and other patients were survival without tumor. Among patients who received simple mastectomy, 3 cases developed a local relapse after 14, 37 and 65 months, respectively; 2 cases were treated with local excision, 1 case was treated with nothing, 1 case received letrozole; 3 patients developed lung metastasis, brain metastases and bone metasta-

sis, respectively; there are 5 patients deaths from breast cancer, 5 patients deaths from other diseases, and other patients were survival without tumor. There were no significant differences between the 2 groups in terms of age, TNM stage, histologic type, histological grade, estrogen receptor (ER), progesterone receptor (PR) and Her-2 (P > 0.05; Table 1). The 5-year cumulative survival rate of the 2 groups were 84.0% and 82.7% respectively; the 5-year recurrence rate were 3.8% and 8.1% respectively, all of them had no significant differences between the 2 groups (P = 0.653 and 0.503; Fig. 1).

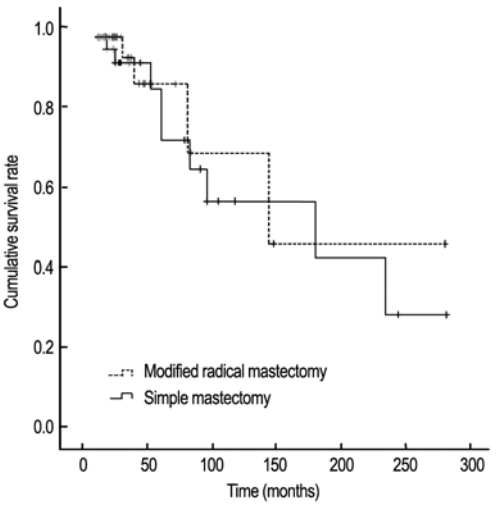

Fig. 1 Survival curves of elderly breast cancer patients received breast surgery

Discussion

Breast cancer incidence increases with age, and as the China population ages, is becoming more common. Comparison to younger, the invasiveness of tumor cells in elderly patients is relatively weak and expression of HER-2 is lower [5]. Noticing the disease course of elderly breast cancer, it makes slower progress than younger. According to ER and PR evaluation, the double positive rate is higher in elderly patients [6]. Similarly, our study indicated that the proportion of elderly patients with ER and PR-double positive is 70.4% (n = 69), and the proportion of double-negative is 11.2% (n = 11). In addition, elderly patients have a great incidence of comorbidity, including pulmonary diseases, cardiac-cerebral vascular diseases and diabetes, and therefore treatment options may differ. Much more elderly patients are less likely to receive breast cancer surgery, radiation or chemotherapy. In this work, the proportion of comorbidity in elder women patients is 65.3%. Currently, there is no standard treatment mode in elderly breast cancer therapy. To decide on the most suitable therapeutic strategy, think about many factors besides age is necessary [6].

The treatment of breast cancer has advanced considerably in the last two decades due to detection technique and especially with the development of alternative surgical approaches [7]. Primary therapy for early-stage breast cancer in elderly people should be modified radical mastectomy. The current evidence established that breast cancer is one of the systemic diseases, so local therapy is not enough. Multiple studies indicated that elderly women should receive less-aggressive surgery, including minimally invasive and fewer axillary dissections. Fisher *et al* [8] reported that lumpectomy followed by breast irradiation continues to be appropriate therapy for women with early breast cancer. Hughes *et al* [9] investigated that Lumpectomy plus adjuvant therapy with tamoxifen alone is a realistic choice for the treatment of women 70 years of age or older who have early, ER-positive breast cancer. Above mentioned studies suggested that modified radical mastectomy plus systemic therapy is an effective treatment for elderly women with early breast cancer. Ge *et al* [10] analyzed the clinical outcome of 166 aged women with breast cancer who were all treated by operation. The overall postoperative 5-year survival rates with I stage or II stage patients were 89.1% and 60.2%, respectively. It is similar that the 5-year survival rates of patients treated with pure mastectomy is 82.7% in our study, however, the 5-year survival rates of modified radical mastectomy group is 84%. There were no statistical differences between two groups who were treated with modified radical mastectomy or pure mastectomy.

Axillary lymph node dissection (ALND) has been recommended treatment for breast cancer patients with early lymph node metastasis. ALND was thought to offer prognostic information, prevent axillary local recurrence, and possibly seriously influence the quality of patients' life by many other postsurgical complications. Martelli *et al* [11] performed a randomized trial comparing axillary dissection to no axillary dissection in older patients with T1N0 breast cancer. Their result suggested that older patients with T1N0 breast cancer can be treated by conservative breast surgery and no axillary dissection without adversely affecting breast cancer mortality or 5-year overall survival rates. Odendaal *et al* [12] indicated that a conservative approach to treating breast cancer patients was adopted for those more than 70 years of age with T1-3 and small localized T4b N0-1 lesions. Tumor excision or simple mastectomy with tamoxifen offers sufficient tumor control for elderly patients. Axillary dissection and breast or chest wall radiotherapy can safely be omitted, thereby greatly reducing health care resource utilization. In our study, pathologic analysis after ALND has been shown that the negative rate of lymph node metastasis is 82.7%, and only 17.3% of all patients with lymph node metastasis. Among them, 8 patients involved 1 to 3 lymph nodes, and one patients had 4 lymph node involving. The

results suggested that the modified radical mastectomy without ALND may be an appropriate therapeutic strategy for elderly breast cancer patients.

Hormonotherapy has certain curative effects and only some slight side effects in breast cancer. Because the expression level of hormone receptor is higher in elderly patients, the hormonotherapy has showed important position of breast cancer treatment. Hughes *et al* [9] investigated that Lumpectomy plus adjuvant therapy with tamoxifen alone is a realistic choice for the treatment of women 70 years of age or older who have early, ER–positive breast cancer. Third-generation aromatase inhibitors have proven to be superior to tamoxifen in terms of time to disease progression in patients with hormone receptor positive status and, nowadays, are used in the adjuvant and neoadjuvant settings and first-line therapy for elderly breast cancer patients. A recent study reported that aged ER+/PR– patients who tend to be resistant to tamoxifen treatment, but has more sensitive to letrozole [13]. Selecting the appropriate chemotherapy for elderly women with resected breast cancer may be the most challenging aspect of treating this patient population. Therefore, it is paramount to weigh the treatment's potential to reduce risk with aged patients' life expectancy independent of breast cancer and the potential toxicity of the therapy. The National Comprehensive Cancer Network has recommended the hormonotherapy to breast cancer patients who aged more than 70 years old if their have hormone receptor positive tumors. But most eventually develop hormone resistance or metastatic breast cancer such as hormone receptor negative or lymph node metastasis, the systemic chemotherapy is required.

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Clinical significance of the negative lymph node count after the axillary dissection of breast cancer patients

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Abstract ***Objective:*** The purpose of this study was to evaluate the impact of the negative lymph node (LN) count on the survival of the breast cancer patients in early stage after the axillary dissection. ***Methods:*** The breast cancer patients with $T_{1-2}N_{0-1}M_0$ stage between January 2001 and December 2005 in Jiangsu Cancer Hospital, who underwent the axillary LNs dissection, were enrolled in this study. We analyzed the data of these patients including information of follow-up and postoperative pathological results. All patients were divided into two groups according to the axillary LN status and each group was divided into four subgroups according to the negative LN count. Cox regression analysis was performed to screen the pathological factor including the negative LN count on the survival and to compare the different negative LN count on the survival. ***Results:*** COX proportional hazard regression model showed that the survival of the breast cancer was significantly associated with the negative LN count. In $T_{1-2}N_0$ group, when the negative LN count was 3 or less, 4 to 5, 6 to 9 and 10 or more, the median survival time was (82.6 ± 4.1) months, (101.5 ± 1.3) months, (104.7 ± 1.0) months, and (110.5 ± 0.9) months respectively ($P < 0.05$). In $T_{1-2}N_1$ group, when the negative LN count was 6 or less, 7 to 8, 9 to 10 and 11 or more, the median survival time was (95.4 ± 1.9) months, (101.8 ± 1.1) months, (104.9 ± 1.0) months, and (106.5 ± 0.9) months respectively ($P < 0.05$). ***Conclusion:*** The negative LN count can reflect the adequacy of the axillary dissection. Increasing negative LN count is independently associated with improved survival in $pT_{1-2}N_0M_0$ or $pT_{1-2}N_1M_0$ staging breast cancer patients. The negative LN count should be considered for incorporation into staging for breast cancer with the axillary LN dissection.

Key words breast cancer; lymph node (LN) dissection; survival analysis

Node status is an important prognostic factor for patients with breast cancer [1, 2]. There is a strong correlation between increasing positive lymph node (LN) count and decreasing prognosis. It is common that the pN stage is divided into four groups according to the positive axillary LN count (0, 1–3, 4–9, ≥ 10 involved nodes). This classification has been introduced by the American Joint Committee on Cancer (AJCC) for the primary therapy of breast cancer [3]. But the pN staging with inadequate number of the axillary LN can not reflect the true LN status. The type of adjuvant systemic therapy and the decision for postmastectomy radiotherapy depend on the accurate pN staging. Some authors investigated the LN ratio excluding the positive LN count, and a prognostic value for the ratio has been suggested [4–7]. The negative LN count is clearly relevant with the number of the LN and the LN ratio. There is comparatively little study on the relationship between the negative LN count and the survival. To improve the understanding of the relationship between the LN count and the survival, we designed this study to examine the impact of the negative LN count on survival of the breast cancer patients with the axillary LN dissection.

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Patients and methods

Patients

From January 2001 to December 2005, 1038 patients with stage $pT_{1-2}N_{0-1}$ breast cancer underwent axillary LN dissection and multidisciplinary treatment. Patients who received preoperative chemotherapy or underwent axilla-conservative surgery were excluded. The tumors were classified as $pT_{1-2}N_{0-1}M_0$ according to the TNM staging system of the AJCC. Patients within each AJCC group ($T_{1-2}N_0M_0$, $T_{1-2}N_1M_0$) were divided into quartiles based on the negative lmph node count. The clinical and histopathological data of the subgroups were collected and entered into a computer database. The histopathological features included the tumor size, pathological categories, tumor differentiation, histological grade, lymphovascular permeation, expression of ER/PR, the negative LN count. All patients were followed up every three or six months

Table 1 Tumor characteristics for patients of breast cancer with stage $T_{1-2}N_0M_0$ or $T_{1-2}N_1M_0$

Characteristics	Total (n = 1038)	AJCC substage	
		$T_{1-2}N_0M_0$	$T_{1-2}N_1M_0$
Tumor size			
T_1	738	492	246
T_2	300	162	138
Pathological categories			
Infiltrating duct carcinoma	977	500	477
Infiltrating lobular carcinoma	30	21	8
Others	31	10	21
Histological grade			
Grade I	134	99	35
Grade II	789	333	456
Grade II	115	35	80
Lymphovascular permeation			
Yes	926	381	545
No	112	62	50
Expression of ER/PR			
Negative	311	182	129
Positive	727	407	320

until December 2010.

Statistical analysis

COX proportional hazard regression model was conducted to identify the independent pathological variables that could influence the survival. The median survival time between quartiles for each substage were compared using the Kaplan-Meier method. Differences between survival curves were tested for statistical significance by the log rank test. All statistical tests were two sided, and P values over 0.05 were considered significant. SPSS Version 10.0 was used for all the statistical analyses.

Results

The study included 1038 women with stage $T_{1-2}N_{0-1}M_0$ breast carcinoma, with a median age of 52 (20–85) years. The pathological variables of each groups including tumor size, pathological categories, tumor differentiation, histological grade, lymphovascular permeation, expression of ER/PR were shown in Table 1.

The patients were divided into quartiles based on the negative LN count (3 or less, 4 to 5, 6 to 9 and 10 or more for $T_{1-2}N_0M_0$ and 6 or less, 7 to 8, 9 to 10 and 11 or more for $T_{1-2}N_1M_0$).

For $T_{1-2}N_0M_0$ staging, Cox regression analysis showed that the T staging, the negative LN count and the expression of hormone receptor were the independent pathological variables impact on the survival time. When the negative LN count was 3 or less, 4 to 5, 6 to 9 and 10 or more, the median survival time was (82.6 ± 4.1) months, (101.5 ± 1.3) months, (104.7 ± 1.0) months, and (110.5 ± 0.9) months respectively (P < 0.05, Fig. 1).

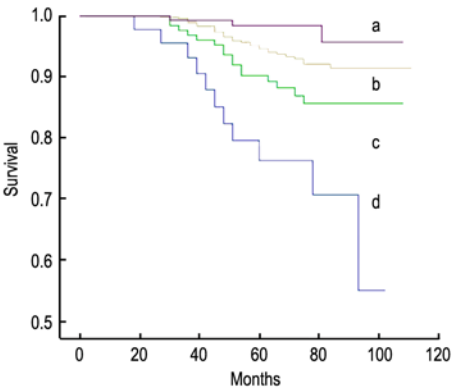

Fig. 1 Survival of $T_{1-2}N_0$ patients with different negative LN count. (a) the negative LN count was 3 or less; (b) the negative LN count was 4 to 5; (c) the negative LN count was 6 to 9; (d) the negative LN count was 10 or more

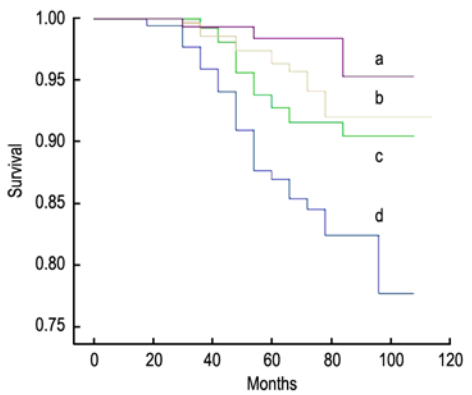

Fig. 2 Survival of $T_{1-2}N_1$ patients with different negative LN count. (a) the negative LN count was 6 or less; (b) the negative LN count was 7 to 8; (c) the negative LN count was 9 to 10; (d) the negative LN count was 11 or more

For $T_{1-2}N_1M_0$ staging, Cox regression analysis also showed that the T staging, the negative LN count and the expression of hormone receptor were the independent pathological variables impact on the survival time. When the negative LN count was 6 or less, 7 to 8, 9 to 10 and 11 or more, the median survival time was (95.4 ± 1.9) months, (101.8 ± 1.1) months, (104.9 ± 1.0) months, and (106.5 ± 0.9) months respectively (P < 0.05, Fig. 2).

Discussion

LN status is well known to be one of the most significant factors influencing prognosis in women with breast cancer [1, 2]. Accurate axillary LN staging can guide the reasonable adjuvant therapy after breast cancer surgery. Although there is an abundance of data to suggest that removal of LN does not affect survival, there is also a wealth

of evidence to suggest that inadequate axillary LN dissection (ALND) in node-positive patients may lead to understaging of the axilla [8, 9]. The adequacy of LN dissection has been touted as a quality measure for breast cancer. A minimum of 10–15 LN is thought to be required to accurately stage the axilla in node-positive patients [10–12]. Although the AJCC has utilized a quantitative classification with 1–3 positive nodes being termed pN_1, 4–9 positive nodes being termed pN_2, and 10 or more positive nodes being termed pN_3 [3], this classification neglects the role of the total LN count and the negative LN count, which also provides additional prognostic information independent of traditional pathologic factors.

We found that for both the subgroups ($pT_{1-2}N_0M_0$ or $pT_{1-2}N_1M_0$), the negative LN count has prognostic value independent of the T staging and the hormone receptor. Increasing negative LN count was independently associated with improved survival in each subgroup. The negative LN count may be able to augment the prognostic ability of the current staging system. Patients underwent ALND not only for local surgical treatment but also to determine disease severity, predict prognosis and influence treatment decision. When the positive LN count was uniform, the negative LN count could provide more accurate prognostic information.

Though the mechanism underlying the relationship between the negative LN count and the survival has not been determined, stage migration may be one of the important reasons. The recently reported American College of Surgeons Oncology Group Z-0011 trial found that 27.3% of non-sentinel LN in the ALND group harbored metastasis [13]. So the LN count can be a marker for the adequacy of surgical treatment. Inadequacy LN count may induce the understaging and would be less likely to receive the proper adjuvant therapies, which would result in the worsening of outcome. Also based on anatomic studies for colon cancer, the LN count is influenced by disease state [14, 15]. It is therefore plausible that interactions between tumor and host might influence the number of assessable LN. Tumor may stimulate the LN to increase in size, which facilitate the ability of the pathologists to detect the nodes. If true, the number of the LN or the negative LN would be a marker of tumor-host interactions, which may have an effect on the survival. It was consistent with our study.

Our study clearly has a number of limitations. Patients in this study were treated in the pre-sentinel LN biopsy era. Some may argue that in the sentinel LN biopsy era, if the sentinel LN is negative, ALND should not be conducted. Although this study did not include patients treated with axilla-conservative surgery, one would anticipate that the negative LN count would be a significant prognostic indicator over and above the current AJCC LN classification alone in the ALND patients. We think that the negative LN count can give more information influencing the prognosis especially for the LN positive patients. We did not evaluate the LN ratio (the proportion of positive LN) as a prognostic variable in our study. Many authors have demonstrated that the LN ratio is an important predictor of survival in breast cancer patients [4–7]. LN ratio and the negative LN count are clearly related and both appear to be important in terms of prognosis. We were not able to incorporate treatment variables which could influence prognosis. Although all the patients received the multi-disciplinary treatment, it would be ideal to evaluate the relationship between the prognosis and the negative LN count in the subgroups with the uniform treatment. These data were not available for this analysis.

In conclusion, we found that increasing negative LN count was independently associated with improved survival in $pT_{1-2}N_0M_0$ or $pT_{1-2}N_1M_0$ staging breast cancer patients. The negative LN count should be considered an alternative to pN staging in ALND breast cancer patients.

Conflicts of interest

All authors declare no conflicts of interest.

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Recent achievements and acute toxicity after TP concurrent chemoradiotherapy for the advanced cervical cancer

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Abstract ***Objective:*** The aim of our study was to investigate the early outcome of the taxotere and cisplatin chemoradiotherapy to the advanced cervical cancer. ***Methods:*** Fifty-six cases with cervical cancer (FIGO IIb to IVa) were divided randomly into two groups in the oncology hospital of Jingzhou from September 2009 to October 2010, radiotherapy alone (28 cases) and radiation plus chemotherapy (TP) group. There was no difference of radiotherapy between the two groups, the RT + C cases who accepted TP regimen during the radiation, and DDP once weekly injection of vain, according to 20 mg/m^2 and taxotere once weekly i.v. according to 35 mg/m^2. These regimen were given for 4–5 weeks, and some medicine for vomiting was given to the RT + C cases. Two groups were received an oral medicine MA 160 mg every day during the treatment. ***Results:*** The early outcome: the complete remission rate was 64.3% and partial remission rate was 35.7% in RT + C. The complete remission rate was 32.1% and partial remission rate was 39.3% in RT. The total response rate and complete remission of RT + C group was higher than that of the RT group. There was significant difference between the two groups. In RT + C group, 1-year survive rate was 100.00% (28/28); in RT group, 1-year survive rate was 85.71% (24/28). There was significant difference between the two groups ($\chi^2 = 4.31 > 3.84$, $P < 0.05$). ***Conclusion:*** The taxotere and cisplatin chemoradiotherapy can improve the early outcome of the advanced cervical cancer, and the adverse effect are raised, but that can be endured.

Key words cervical cancer; taxotere; cisplatin; chemoradiotherapy

Cervical cancer is the most common gynecologic cancer. Surgery or radiotherapy can achieve satisfactory effect for early stage cervical cancer, while in the late stage (IIb–IVa period) the main treatment therapy is radiation. At present, many studies all over the world reported that radiotherapy combined with chemotherapy can improve the survival rate of patients with cervical cancer. Fifty-six patients with cervical cancer in IIb–IV stage, who hospitalized in oncology unit from September 2009 to October 2010, were randomly divided into chemoradiotherapy group and radiotherapy group. The comparison of two groups is as follows.

Materials and the methods

Samples

All cases were pathologically confirmed in IIb–IV stage, according to FIGO staging [1] and in their initial treatment. They all had KPS ≥ 70 points. Before treatment, their blood routine, liver and kidney function and ECG were normal. These 56 patients were randomly divided into two groups: radiotherapy (RT group) 28 cases, concurrent chemoradiotherapy group (RT + C group) 28 cases in the oncology hospital of jingzhou from September 2009 to October 2010 with the Ethical Approval. Patients' characteristics were shown in Table 1. There is no statistically significant in the difference between the two groups on general characteristics, past history and clinical performance.

Treatment

They all accepted the 15 Mv X-ray of 23-EX Varian linear accelerator and Ir^{192} high dose rate brachytherapy. The treatment to the pelvic was the first. The brachytherapy and the 4 beams radiotherapy to the pelvic were fulfilled simultaneously after the center of the pelvic got 40 Gy/20 f/4 weeks. The brachytherapy was fulfilled once a week, which gave the A point 6 Gy, the total doses 18–30 Gy. At the same time, the 4 beams to the pelvic gave the parauterus 10–16 Gy, 2 Gy every time. And the two methods didn't happen on the same day. The upper bound of the exobody radiotherapy was L4–L5, the low

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Table 1 Characteristics of samples

Group	Cases	Age (years)		Pathological type		Clinical stage			
		Range	Median	SCC	Adenocarcinoma	IIb	IIIa	IIIb	IVa
RT	28	34–65	54	20	8	6	12	6	4
RT + C	28	33–64	53	21	7	7	13	5	3

SCC: squamous cell carcinoma

Table 2 Comparison of treatment effect

Group	*n*	CR		PR		NC		PD	Efficient (%)
		n	%	*n*	%	*n*	%		
RT	28	9	32.1	11	39.3	8	28.6	0	71.4
RT + C	28	18	64.3	10	35.7	0	0	0	100.0

$\chi^2 = 9.33 > 3.84$; $P < 0.05$

upper bound was lower margin of the obturator foramen, and the outer margin was 2 cm to the real pelvic.

RT + C group began with a weekly radiation therapy used cisplatin 20 mg/m^2 i.v. drop d1 and docetaxel 35 mg/m^2 intravenously d1 for 4–5 weeks. Routinely antiemetic drugs and proper hydration used and oral dexamethasone used for anti-allergic reaction.

Both two groups of patients were taking megestrol acetate 160 mg everyday from the start of treatment to the end of treatment.

Monitoring

The items need to be evaluated and monitored are clinical symptoms and signs, adverse reactions, blood tests every week, vaginal speculum examination once a week, electrocardiogram before and after treatment, liver and kidney function and related imaging tests before and after treatment, record tumor size (maximum diameter and the anteroposterior diameter), parametrial invasion; Tumor shrinkage percentage = (Volume before radiotherapy – Radiotherapy volume) / Volume before radiotherapy, after three months of treatment, efficacy and toxicity.

Statistics analysis

χ^2 test was used to compare efficient and incidence of side effects in two groups.

Results

Effect of treatment

According to general standard for solid tumor treatment efficacy [1], the outcome of treatment divided into complete remission (CR), partial remission (PR), stable (NC) and deterioration (PD). Recent cancer treatment efficacy was shown in Table 2.

In RT group: CR 9 cases are squamous cell carcinoma, PR 11 cases are squamous cell carcinoma, NC 8 cases are adenocarcinomas; in RT + C group: CR 17 cases are squamous cell carcinoma, 1 case of adenocarcinoma. PR 4 cases are squamous cell carcinoma, 6 cases of adenocarcinoma; two groups compared, RT + C group's squamous cell carcinoma CR was significantly higher than that of RT group, the difference was statistically significant ($\chi^2 = 5.71 > 3.84$; $P < 0.05$); RT + C group's adenocarcinoma effective rate (CR + PR) was significantly higher than the RT group, the difference was statistically significant ($\chi^2 = 15 > 3.84$; $P < 0.05$). In RT + C group, 1-year survive rate was 100.00% (28/28); in RT group, 1-year survive rate was 85.71% (24/28). There was significant difference between the two groups ($\chi^2 = 4.31 > 3.84$; $P < 0.05$).

Acute toxicity

(1) Mainly reaction are fatigue, loss of appetite, stool frequency increased. Few cases have nausea, vomiting, stool sense of falling, urinary urgency, frequent urination. (2) Hematological toxicity: according to common grading criteria of anticancer drugs toxicity [2]. RT group has 8 patients with grade I myelosuppression and no grade II, III degree, IV myelosuppression. RT + C group has 14 cases with grade I myelosuppression, 7 cases with grade II myelosuppression in, 2 cases with grade III myelosuppression and no grade IV myelosuppression, ($\chi^2 = 16.29 > 3.84$, $P < 0.05$). Subcutaneous injection of recombinant human granulocyte colony stimulating factor were given for grade I, II, III myelosuppression. Before and after treatment, patients within both two group have their liver and renal function, ECG normal.

Discussion

Cervical cancer is one of the common gynecologic malignancies. It is a very important issue in gynecology. Radiation therapy is an effective choice for advanced cervical cancer treatment, but radiotherapy effect itself is not satisfactory, therefore, the U.S. National Cancer Institute (NCI) in February 1999 announced to the world, that the combination of radiotherapy and chemotherapy treatment at the same time in advanced cervical cancer

have good effect and suggested for patients who received radiotherapy, chemotherapy should be given the same time [3]. Recent studies confirmed that concurrent radiotherapy and chemotherapy in advanced cervical cancer is safe and feasible, have good effect.

Chemotherapy drug cisplatin is not only has the ability to kill tumor cells, but also can sensitize the effect of radiation and inhibit the repair of radiation damaging cells. The American National Cancer Institute stated cisplatin-based concurrent chemoradiotherapy as the standard treatment for locally advanced cervical cancer and early stage high-risk cervical cancer [4]. Pignata [5] used paclitaxel and cisplatin with concurrent chemoradiotherapy achieved initial results. Docetaxel and cisplatin used with concurrent chemoradiotherapy in this study get more effective sensitized, the reason is the radiotherapy major role in the G1, M phase, while the chemotherapy drug cisplatin is non-specific drugs for cell cycle, which could kill cells in all stages, specific drugs Taxotere major role in the M phase, these three have synergistic effect. Two groups have radiation in the same manner. RT + C group had the recent efficacy rate at 100.0%, RT group was 71.4%. Specially in CR cases, RT + C had 18 patients, RT group had 9 patients with significant difference ($\chi^2 = 9.33 > 3.84$; $P < 0.05$). Compared the two groups, RT + C group was significantly higher at squamous cell carcinoma CR than that of RT group, the difference was statistically significant ($\chi^2 = 5.71 > 3.84$; $P < 0.05$); RT + C group for adenocarcinoma effective (CR + PR) was significantly higher than RT group, the difference was statistically significant ($\chi^2 = 15 > 3.84$; $P < 0.05$). In RT + C group, 1-year survive rate was 100.00% (28/28); in RT group, 1-year survive rate was 85.71% (24/28). There was significant difference between the two groups ($\chi^2 = 4.31 > 3.84$; $P < 0.05$).

Paclitaxel and cisplatin used in concurrent chemoradiation for cervical squamous cell carcinoma and adenocarcinoma were increased efficacy, particularly more pronounced sensitizing effect of cancer, but in this study a small number of cases with adenocarcinoma may make the limitation. Study on large number of cases still needs to be done. Toxicity compared two groups: the recent reaction of fatigue, loss of appetite, RT + C group emphasis without statistically significant, which did not affect the treatment. Hematological toxicity: the incidence in RT + C group was 82.1%, grade I, grade II and grade III myelosuppression required recombinant human granulocyte colony stimulating factor treatment, but no grade IV myelosuppression; RT group had light hematologic toxicity, the incidence was 28.6% with grade I myelosuppression. Compared two groups, the difference between incidence was statistically significant ($\chi^2 = 16.29 > 3.84$; $P < 0.05$). The toxicity in two groups could be tolerated, which may be related to taking progesterone, researches have shown that megestrol acetate significantly assisted the role of cancer chemotherapy to increase food taken, reduce gastrointestinal side effects of chemotherapy, improve the role of quality of life [6]. This study shows that docetaxel and cisplatin in concurrent chemoradiotherapy in advanced cervical cancer has a good short-term effect, but also increased the toxicity, but it can be tolerated after taking megestrol acetate. The sample size in this study is small with a short time follow up. The long-term effect needs further observation.

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Hematologic toxicity of gemcitabine: a comparison between fixed-dose rate infusion and thirty-minute infusion in the treatment of malignancy*

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Abstract ***Objective:*** The aim of the study was to compare the hematologic toxicity of gemcitabine between fixed-dose rate (FDR) infusion and 30-minute standard infusion in the treatment of malignancy. ***Methods:*** The 25 malignancy patients confirmed by histopathology or cytology received single-agent gemcitabine or gemcitabine in combination with other chemotherapeutic agents. These patients were randomly divided into gemcitabine 1000 mg/m^2 on d1, d8 at a rate of 10 mg/m^2/min arm (FDR arm) or 30 min arm (standard arm), every 21 days one cycle. Hematologic toxicity was evaluated at the end of each cycle. ***Results:*** The 13 of 25 patients received gemcitabine FDR therapy, a total of 28 cycles was completed, and 32 cycles in the others (12 of 25 patients) with the standard arm. All patients were evaluable for hematologic toxicity. The result showed that the grades 3–4 leucopenia was significantly different between the two arms (14.3% vs 0, $P < 0.05$), and no significant differences of neutropenia, thrombocytopenia and hemoglobin suppression of grades 3–4 (14.3% vs 3.1%, 10.7% vs 3.1%, 3.6% vs 9.4%, $P > 0.05$, respectively) were observed between the two arms, no grade 4 of hemoglobin suppression was observed. ***Conclusion:*** Hematologic toxicity of gemcitabine therapy at a fixed-dose rate for malignancy is tolerable.

Key words gemcitabine; fixed-dose rate (FDR); malignancy; hematologic toxicity

As a commonly used chemotherapeutic agent, gemcitabine is usually given at a dose of 1000 mg/m^2/30 minutes intravenously. Single-agent gemcitabine and in combination with other chemotherapeutic agents were effective in lung cancer, head and neck neoplasms, breast cancer, ovarian cancer, pancreatic cancer and sarcoma, etc. In 1997, gemcitabine was approval to patients with advanced pancreatic cancer by the FDA of United States, and then as well as patients with advanced breast cancer, lung cancer and ovarian cancer.

The pharmacokinetics study shows that with the increased plasma level of gemcitabine by the increased administration cycles and the administration time the efficacy improves. In recent years, an increasing number of clinical trials researched the efficacy and side effects of gemcitabine with fixed-dose rate (FDR) infusion in various malignancy, most of the studies show that FDR infusion can improve the efficacy of gemcitabine through prolonged administration time, but meantime, the side effect increased, especially the grade 3 hematological toxicity. Our research compared the hematological toxicities between fixed-dose rate infusion arm and thirty-minute infusion arm of gemcitabine during treating with malignancy.

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Patients and methods

Clinical data

A total of 25 patients with histopathologic or cytologic diagnosis of malignancy were enrolled between February 2009 with May 2010 in our Hospital (Tenth People's Hospital, Tongji University, Shanghai, China) and had received prior at least one cycle gemcitabine treatment. All of them were evaluated for eligibility. The 13 of 25 patients received gemcitabine FDR therapy, a total of 28 cycles was completed, and 32 cycles in the others (12 of 25 patients) with the standard arm. More details of these 25 patients were outlined in Table 1.

Table 1 Patient characteristics

Characteristics	FDR arm (*n*)	Standard arm (*n*)
Patients entered	13	12
Cycle number	28	32
Sex		
Male	5	11
Female	8	1
Age (years)		
Median	56	60.5
Range	48–86	34–80
Diagnosis		
Lung cancer	6	6
Nasopharyngeal carcinoma	1	2
Pancreatic cancer	0	2
Gallbladder carcinoma	1	0
Bladder cancer	1	2
Ovarian cancer	1	0
Endometrial carcinoma	1	0
Peritoneal carcinoma	1	0
Salivary gland carcinoma	1	0
Clinical stage		
Stage I	1	0
Stage II	1	1
Stage III	2	1
Stage IV	9	10

Treatments

All patients received chemotherapeutic regimens which contained gemcitabine, given at the dose of 1000 mg/m^2 intravenously on d1, d8. The fixed-dose rate infusion of gemcitabine (FDR GEM) was at a rate of 10 mg/m^2/min. The standard arm was with a total time of 30 minutes. The cycle was repeated every 21 days. Before the treatment, the antiemetic agents, such as the ondansetron hydrochloride injection or tropisetron hydrochloride injection were used. Those who received the gemcitabine in combination with cisplatin regimen were treated with the dexamethasone. During the chemotherapy, the grades 3–4 bone marrow suppression would be treated by G-CSF or IL-11, blood transfusion would be treated if necessary. The severe bone marrow suppression was dangerous, if the absolute neutrophil count (ANC) was at the range of 0.5×10^9/L–1.0×10^9/L or platelet count was at the range of 50×10^9/L–100×10^9/L, the dose of gemcitabine was reduced by 25%; if the absolute neutrophil count < 0.5×10^9/L or platelet count < 50×10^9/L, the gemcitabine was omitted.

Hematologic toxicity

Response to treatment was assessed according to World Health Organization (WHO) criteria. Hematologic toxicity was evaluated at the end of each cycle.

Statistical analysis

Applying χ^2 inspection and FISHER exact test to analysis the data, and P value < 0.05 was defined statistical significance.

Results

There were 25 patients with histopathologic or cytologic diagnosis of malignancy. The 13 of 25 patients received gemcitabine FDR therapy, a total of 28 cycles was completed, and 32 cycles in the others (12 of 25 patients) with the standard arm. Hematologic toxicity was evaluated at the end of each cycle.

In FDR GEM arm, the grades 3–4 adverse events were the grade 3 leukopenia 10.7% (3/13), the grade 4 leukopenia 3.6% (1/13), the grade 3 neutropenia 7.1% (2/13), and the grade 4 neutropenia 7.1% (2/13). While in the standard arm, no grades 3–4 leukopenia was reported, and the grade 3 neutropenia only 3.1% (1/12). In FDR arm, the rates of leukopenia and neutropenia were obviously higher than those of the standard arm (P < 0.05). In addition, In FDR GEM arm, 10.7% (3/13) patients received the platelet transfusion because of the grade 4 thrombocytopenia, and no treatment-related death. In the standard arm, 3.1% (1/12) patients had the grade 3 thrombocytopenia. But there was no differences between the two arms in the level of anemia and thrombocytopenia (Table 2).

The result showed that the two arms met the pre-specified criteria (the significance level of 5%) for significance (14.3% vs 0%, P < 0.05) in the rates of grades 3–4 leukopenia, while the rates of neutropenia (14.3% vs 3.1%, P > 0.05), anemia (10.7% vs 3.1%, P > 0.05), thrombocytopenia (3.6% vs 9.4%, P > 0.05). Neither of these differences met the pre-specified criteria for significance (Table 3).

Discussion

Gemcitabine is a nucleoside analog that has therapeutic activity against lung, breast, pancreatic, bladder, ovarian and hematological malignancies. Gemcitabine diphosphate blocks DNA synthesis by inhibiting ribonucleotide reductase, the enzyme responsible for production of deoxynucleotides required for DNA replication and repair. This inhibition results in lower level of deoxycytidine triphosphate (dCTP) and high level of gemcitabine triphosphate (dFdCTP) accumulation. Gemcitabine triphosphate is then incorporated into newly synthesized DNA, thereby causing masked-chain termination that interferes with excision repair of the gemcitabine monophosphate from the DNA [1].

The phosphorylation of gemcitabine triphosphate by deoxycytidine kinase is a rate-limiting step [1–3], and

Table 2 The comparison between FDR arm and the standard arm in bone marrow suppression

Bone marrow suppression	Grade 0		Grade 1		Grade 2		Grade 3		Grade 4		χ^2	*P*
	n	%	*n*	%	*n*	%	*n*	%	*n*	%		
Leukopenia											13.915	0.008
FDR-A	10	35.7	8	28.6	6	21.4	3	10.7	1	3.6		
Standard-A	25	78.1	2	6.2	5	15.6	0	0	0	0		
Low hemoglobin											1.035	0.793
FDR-A	12	42.9	9	31.2	6	21.4	1	3.6	0	0		
Standard-A	14	43.8	10	52.6	5	15.6	3	9.4	0	0		
Thrombocytopenia											6.144	0.189
FDR-A	23	82.1	0	0	2	7.1	0	0	3	10.7		
Standard-A	26	81.2	2	6.2	3	9.4	1	3.1	0	0		
Neutropenia											12.689	0.013
FDR-A	14	50.0	5	17.9	5	17.9	2	7.1	2	7.1		
Standard-A	29	90.6	1	3.1	1	3.1	1	3.1	0	0		

Table 3 The comparison between FDR arm and the standard arm in bone marrow suppression with FISHER exact test

	Grades 0–2		Grades 3–4		*P*
	n	%	*n*	%	
Leukopenia					0.042
FDR-A	24	85.7	4	14.3	
Standard-A	32	100.0	0	0	
Low hemoglobin					0.616
FDR-A	27	96.4	1	3.6	
Standard-A	29	90.6	3	9.4	
Thrombocytopenia					0.331
FDR-A	25	89.3	3	10.7	
Standard-A	31	96.9	1	3.1	
Neutropenia					0.175
FDR-A	24	85.7	4	14.3	
Standard-A	31	96.9	1	3.1	

deoxycytidine kinase had reached saturation when gemcitabine was in a low concentration. These studies found that the maximal triphosphate accumulation in the monocytes and leukemia cells was associated with the plasma concentration of gemcitabine, which was 20 mol/L in the FDR (10 mg/m^2/min) infusion patients. Based on these studies, the relationship between treatment time and cycles with clinical efficacy was explored in more and more clinical trails.

In the Version 1, 2009 of NCCN Guideline for Pancreatic Cancer, the regimen of fixed-dose rate infusion of gemcitabine (FDR GEM) was also recommended as the prior regimen to gemcitabine thirty-minute infusion (standard arm) by the panel (2B) [4]. Many studies exploring gemcitabine treatment with patients of pancreatic cancer can be found. Tempero *et al* [5] randomly divided 92 pancreatic cancer patients who were enrolled onto this study into one of the following two arms: fixed-dose rate infusion and thirty-minute infusion. The results showed the cells of patients who received the FDR infusions accumulated gemcitabine triphosphate to approximately twice the concentration generated by the standard arm, though the dose of FDR GEM was only 68% of the standard arm's. The clinical results showed that higher proportion patients experiencing improvement in PS in the FDR arm (27.3% vs 9.1%), but with more hematologic toxicity. Not one, Eastern Cooperative Oncology Arm compared the overall survival and side effects among three teams: gemcitabine in combination with oxaliplatin, the fixed-dose rate infusion arm (FDR arm) and thirty-minute infusion arm (standard arm) in a phase III clinical trial of 832 patients [6]. The results showed that the median survival times of the combination arm and the FDR arm were slightly higher than that of the standard arm, but there is not the statistically significant difference. In the FDR arm, the proportion of grades 3–4 leukopenia and thrombocytopenia was the highest. Another study [7] in 2009, 259 patients were randomly assigned to one of the following four arms: gemcitabine in combination with cisplatin, fixed-dose rate infusion of gemcitabine arm, gemcitabine in combination with docetaxel and gemcitabine in combination with irinotecan. Comparing the response rate, toxicity and the survival time, the results showed neither of their differences met the pre-specified criteria for significance among the four arms. A study [8] in 2010 recommended the regimens of fixed-dose rate infusion of gemcitabine as a first-line option in advanced pancreatic and biliary tract cancer.

In two phase II clinical trials about the fixed-dose rate infusion regimen (FDR GEM arm) or thirty-minute infusion regimen (standard arm) in treatment with the non-small cell lung cancer, their results were opposite. One study [9] showed the FDR GEM was more effective, but the other study showed their efficacy was similar [10]. Moreover, the proportion of grades 3–4 neutropenia in the FDR GEM was obviously higher than standard arm (49.2% vs 17.9%), grades 3–4 thrombocytopenia in the FDR GEM also was higher (9.9% vs 1.8%). The efficacy and toxicity of the fixed-dose rate infusion of gemcitabine

in combination with oxaliplatin (GEMOX) in treating 40 non small lung cancer patients were observed in a study of 2008 [11]. The result showed the regimen was active and well tolerable. The most common grades 3–4 hematological toxicity was leukopenia, nearly 20%. Caffo *et al* [12] observed the pharmacokinetics of the fixed-dose rate infusion of gemcitabine in combination with cisplatin in advanced non small cell lung cancer patients. Studies showed a higher accumulation of gemcitabine metabolite in peripheral blood mononuclear cells was observed when the longer infusion time was employed.

In the past two years, the efficacy and side effects of many clinical trails of gemcitabine in combination with other chemotherapeutic agents had also been observed. Such as, the fixed-dose rate infusion of gemcitabine (FDR GEM) in combination with erlotinib in the pancreatic cancer patients was active and well tolerable [13]. The FDR GEM in combination with paclitaxel was active and safe regimen for advanced breast cancer patients pretreated with anthracyclines [14]. The FDR GEM in combination with carboplatin in relapsed, platinum-sensitive ovarian cancer patients also was active [15]. The FDR GEM in combination with pemetrexed was active in a broad range of advanced solid tumors types, including gastric cancer, pancreatic cancer, biliary tract cancer, colon cancer, non-small cell lung cancer, hepatocellular carcinoma, bladder cancer and others [16].

Our research compared the hematologic toxicity between gemcitabine in fixed-dose rate infusion (10 mg/m^2/min) with thirty-minute infusion during treatment with lung cancer, gallbladder cancer, cardiac cancer, salivary gland cancer, ureter cancer, and bladder cancer. The result showed that the two arms met the pre-specified criteria (the significance level of 5%) for significance (14.3% vs 0%, $P < 0.05$) in the rates of grades 3–4 leukopenia. While neither of the differences of neutropenia (14.3% vs 3.1%, $P > 0.05$), anemia (10.7% vs 3.1%, $P > 0.05$), thrombocytopenia (3.6% vs 9.4%, $P > 0.05$) met the pre-specified criteria for significance. In FDR arm, 10.7% (3/13) patients received the platelet transfusion because of the grade 4 thrombocytopenia.

In the present study, grade 4 thrombocytopenia in the FDR GEM arm was observed in 3 patients. Respectively, patient 1 is a gallbladder cancer patient, female, accepting a long-term traditional Chinese medicine without chemotherapeutic agents in another hospital. She received the FDR GEM in combination with oxaliplatin in our hospital after recurrence and metastasis in our department. After the chemotherapy, a severe thrombocytopenia was observed, the lowest platelet level was 4×10^9 /L. After treatment of the platelet transfusion and IL-11 intramuscular injection, the platelet account recovered.

Patient 2 was an advanced lung cancer patient, female, who had receiving several cycles of TP regimen and the radiation therapy about her brain and lung. After adrenal gland and liver metastasis, she received the FDR GEM in combination with cisplatin regimen. After the treatment, severe thrombocytopenia of the lowest platelet count 3×10^9/L and the leukopenia of 0.7×10^9/L with urinary occult blood (2+) were observed, without subcutaneous petechia/ecchymosis and nasal bleeding. After the IL-11, GSF intramuscular injection and the platelet transfusion, the hemogram recovered.

Patient 3 was an ovarian cancer patient, female, who had received nine cycles of paclitaxel in combination with cisplatin regimen in all, the chemotherapeutic regimens swifted to the FDR GEM in combination with nedaplatin because of the severe sacral pain. After the treatment, a severe thrombocytopenia was also observed, the lowest platelet count was 10×10^9/L, with a slight vaginal bleeding, urinary occult blood test (1+), without subcutaneous bleeding or gross hematuria. After the IL-11 intramuscular injection and the platelet transfusion, the hemogram also recovered.

Before the combination chemotherapy, the three patients had received long-term Chinese medicine treatment or chemotherapy to be the weak bone marrow function. There was no sufficient evidence for the conclusion that the grade 4 thrombocytopenia was directly related with the FDR GEM regimen. Besides, treatment-related death had not been found.

In summary, the hematologic toxicity of gemcitabine at the fixed-dose rate infusion is tolerable. The efficacy of single-agent gemcitabine and in combination with other chemotherapeutic agents still need the further observation. In consideration of the grade 4 thrombocytopenia, dose reduction can be made, but further study is needed to determine the efficacy of the milder regimen.

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Clinical application of OxyContin hydrochloride controlled release tablets in treatment of pain suffered from advanced cancer

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Abstract ***Objective:*** The aim of this study was to evaluate the efficacy and adverse reactions of OxyContin hydrochloride controlled release tablets in the treatment of moderate or severe pain in patients with terminal cancer and to observe any improvement on the cancer patients' quality of life. ***Methods:*** Sixty-eight patients with moderate or severe cancer pain were treated with OxyContin hydrochloride controlled release tablets. The initial dose was 5 mg/12h, or 1/2 that of the standard morphine regimen. During the course of treatment, the dosage was adjusted according to the patients' condition until the pain completely disappeared or nearly did so. Each patient received a treatment for at least 15 days. At the same time, adverse reactions, the quality of life and scores for the intensity of pain were observed and recorded [1]. ***Results:*** The final titrated dosage of OxyContin was as follows: the patients in 30 cases (44.1%) received a dosage of ≤ 30 mg/d, those in 16 cases (23.5%) received a dosage of 31 to 60 mg/d, those in 18 cases (26.5%) received a dosage of 61 to 120 mg/d and those in 4 cases (5.9%) received a dosage of ≥ 120 mg/d. The overall rate of relief from pain was 95.6%, among which the rates of excellent, effective and moderate relief were respectively 39.7%, 48.5% and 7.4%. OxyContin had mild adverse reactions and patients' quality of life was markedly improved. ***Conclusion:*** OxyContin is effective in treatment of moderate and severe cancer pain. The adverse reactions of OxyContin are mild, and the drug can significantly improve the quality of life of patients with cancer pain.

Key words advanced cancer; pain; OxyContin

Pain is a common symptom for patients with advanced cancer, with its incidence of as high as 60%–90%. There are nearly 9 million people suffering from cancer pain each year in the world. Prior to 2021 the said number of people will be increased to 15 million. Cancer pain tremendously influences patients' quality of life (QOL). Thus, analgesia treatment is of great significance [1]. OxyContin hydrochloride controlled release tablets (trade name: OxyContin) is a new type of potent narcotic analgesics of opium types, the main characteristics of which lies in its immediate-release and controlled release. It possesses the function of a rapid effect and a whole course controlled release [2]. The hospital used OxyContin in the treatment of 68 cases of moderate or severe pain in patients with cancer from August 2005 to November 2006 and achieved a satisfactory analgetic effect.

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Materials and methods

Clinical data

In the group, there were 36 males and 32 females, aged from 29–72 years, with median age of 51.4 years. All patients were at phase IV according to TNM classification. The primary tumor of various kinds were as follows: 22 cases of breast cancer, 18 cases of lung cancer, 12 cases of gastric cancer, 10 cases of colorectal cancer, 4 cases of liver cancer and 2 cases of pancreatic cancer.

Pain intensity and nature determination

Pain intensity was determined by numeric rating scale (NRS) [3]. A number between 0–10 was selected by patients themselves in order to determine the corresponding pain intensity. All the cases of pain prior to treatment were assessed to be moderate or severe, of which there were 18 cases of moderate pain (26.5%) and 50 cases of severe pain (73.5%). The pain intensity was classified in the light of clinical symptoms and physical examinations into somatic pain, visceral pain, neuralgia and two

or more than two kinds of mixed pain, with respectively 20 cases (29.4%), 38 cases (55.9%), 2 cases (2.9%) and 8 cases (11.8%).

Methods of treatment

OxyContin controlled release tablets: 10 mg/tablet. For those patients who had not used any analgesics or those who had used weak opium analgesics, the initial dose was 10 mg, 2 times per day. For those patients who were using morphine analgesics, the initial dose was 1/2 that of the standard morphine regimen. Afterwards, the drug dosage to be used was adjusted in accordance with the condition of the disease until the ideal analgesics effect was obtained. Each patient was treated that way for at least more than 15 days.

Determination of therapeutic effects

(1) Pain remission degree and pain relief rate.

Pain remission degree: 0 degree: pain was not relieved; 1 degree: mild remission (about 1/4); 2 degree: moderate remission (about 1/2); 3 degree: obvious relief (pain relieved about over 3/4); 4 degree: complete remission (pain disappeared).

Pain relief rate: the rate referred to the moderate and the above moderate pain relief rate (the percentage of the No. of patients whose pain was relieved by 2 degree or above in the all cases)

(2) The score of the QOL.

A scoring was conducted of the QOL of cancer patients by reference to the score draft which had recorded such score methods in five aspects as appetite, sleep, daily life, mental status and interpersonal intercourse before and after medication, and a subsequent comparison was carried out accordingly.

(3) Observation and records of adverse reactions.

Statistical analysis

All the data was analyzed with SPSS statistical software. $P < 0.05$ was of statistical difference.

Results

Titration analysis of different dosage

The initial dose of OxyContin was 10–120 mg/d. For 45 cases (66.2%) the dose was ≤ 30 mg/d, for 12 cases (17.6%) 31–60 mg/d, and for 11 cases (16.2%) 61–120 mg/d. There were 38 cases (55.9%) among the above where the dosage required to be adjusted, with an adjustment range of from 10 mg to 80 mg. It was so found out that after the dosage adjustment most of the patients obtained satisfactory analgetic effect. The final titrated dosage of oxyeodone was as follows: the patients in 30 cases (44.1%) received a dosage of ≤ 30 mg/d, those in 16 cases (23.5%) received a dosage of 31 to 60 mg/d, those in 18 cases (26.5%) received a dosage of 61 to 120 mg/d and those in 4 cases (5.9%) received a dosage of ≥ 120 mg/d.

Table 1 The cancer pain remission degree of patients (*n*)

Pain degree	Cases	Pain remission degree					Pain relief rate (%)
		0	1	2	3	4	
Moderate	18	0	0	1	5	12	100.0
Severe	50	1	2	4	28	15	94.0
Total	68	1	2	5	33	27	95.6

Table 2 The changes of QOL pre- and post treatment ($\bar{\chi} \pm s$)

QOL	Pre- treatment	Post treatment	*P*
Appetite	1.95 ± 0.51	3.08 ± 0.45	< 0.01
Sleep	1.96 ± 0.56	3.48 ± 0.67	< 0.01
Daily life	1.78 ± 0.51	3.12 ± 0.61	< 0.01
Mental status	1.69 ± 0.51	3.18 ± 0.64	< 0.01
Interpersonal intercourse	2.01 ± 0.45	3.15 ± 0.67	< 0.01

Analysis of therapeutic effect

A summary and statistics of therapeutic effect for all the patients on the 15th day of medication was shown in Table 1 .

After medication of OxyContin in treatment, moderate or more remission (100.0%) was observed in patients with moderate cancer pain in 18 cases, of which 12 cases (66.7%) were of a complete remission and 5 cases (27.8%) of obvious relief. While in the 50 cases where the patients suffered from severe pain, moderate or more remission (100.0%) of cancer pain were obtained in 47 cases (94.0%), of which 15 cases (30.0%) saw a complete remission and an obvious pain relief was acquired in 28 cases (56.0%). The clinical data showed that OxyContin had a good therapeutic effect on remission of the pain originated from breast cancer, lung cancer, gastric cancer, colorectal cancer, liver cancer and pancreatic cancer. Also, the said drug had a good effect on the various types of cancer pain in the forms of visceral pain, somatic pain, neuralgia and mixed pain, etc.

Analysis of the QOL

A scoring of the patients' QOL after treatment with OxyContin for 15 days was conducted and a comparison was carried out with the score recorded before the treatment (Table 2).

The patients' appetite, sleep, daily life, mental status and interpersonal intercourse markedly improved, with a significant difference before and after treatment ($P < 0.01$).

Observation of adverse reactions

Such adverse reactions as constipation, nausea and vomiting, dizziness and dysuria, etc. were observed in the patients under treatment. Except for constipation, the ad-

verse reactions were of low occurrence probability. After symptomatic treatment, constipation was alleviated and the other adverse reactions gradually disappeared with the time prolonging with medication. Psychological dependence, serious adverse events or drug abuse were not observed in any of the above.

Discussion

Three-step analgesic ladder to treat cancer pain recommended by WHO has put forwarded that the main method for treatment of cancer pain is analgesia treatment with drugs. Opioids are the main drugs in treatment of cancer pain [4–8]. OxyContin hydrochloride is metabolized by 0-demethylation to oxymorphone and nor-OxyContin, with a significant opium agonist activity and the highest bioavailability among the commonly-used opioid drugs. The strength of analgesia of OxyContin hydrochloride is about two times that of morphine [9, 10]. OxyContin is the perfect combination of the Acrocontin Company's technology and OxyContin hydrochloride. The immediate release that accounts for 38% in the drug composition makes an analgesia effect obvious within one hour after it is taken, while the control release accounting for 62% in the composition makes the analgesia effect sustained and ensures a stable pain control for twelve hours with a durable plasma concentration. We have used OxyContin in treatment of 68 cases of moderate or severe cancer pain with a severe pain relief rate of 94% (47/50) and a total pain relief rate of 95.6% (65/68), among which complete remission was acquired in 27 cases (39.7%), significant relief in 33 cases (48.5%) and moderate relief in 5 cases (7.4%). So we hold that a satisfactory analgesia effect ties in a strict control of the individual dosage titration. In treatment of 68 cases, 38 cases (55.9%) is required for dosage adjustment, the dosage adjustment range being controlled from 10 mg to 80 mg. By means of the dosage adjustment in a timely manner, 40 cases (58.8%) achieve to a marked analgetic effect one day after medication and 58 cases (85.3%) to a sustained stable analgetic effect five days after drug usage. The half-life of OxyContin is relatively short so that a steady-state concentration is acquired after drug usage 2–3 times, rendering the dosage titration an easy job. In view of OxyContin consisting of the immediate release that accounts for 38% in its composition, the plasma concentration is made elevated very quickly with the drug resulting in a relatively shorter time between drug-taking and effect-gaining than with other opioid analgesics so as for the application of morphine injection to be cut back. In addition, the usage of OxyContin can cause patients to increase their confidence in orally administered drugs in treatment and also lighten their suffering. It may be noted that in regard to different cancers or natures of cancer pain, OxyContin is always of a good therapeutic effect in clinical treatment of tumors and cancer pain of various kinds. The present study shows that OxyContin is an effective drug for cancer pain with a satisfactory therapeutic result in that the patients not only experience a considerable alleviation of pain but also acquire an enhancement of their QOL, especially, an improvement of sleep quality. Furthermore, there are fewer adverse reactions with OxyContin treatment, which mostly occurs during the initial stage of medication. With the prolonging of time when the drug is gradually tolerated by the body, the incidence of the adverse reactions reduced by degrees. The occurrence of adverse reactions is not in direct proportion to drug dosage. Of the adverse reactions, constipation is rather stubborn and tricky, but it can be significantly relieved with a concurrent usage of Chinese medicine for constipation.

In summary, OxyContin is a high efficient analgesic in treatment of moderate or severe cancer pain with a satisfactory efficacy because of its practicality, simplicity, convenience and safety in use and fewer adverse reactions. It can also improve patients' QOL and heighten patients' confidence in further treatment. Therefore, OxyContin is worth popularizing in clinical therapy.

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Right iliac fossa abscess as first manifestation of perforated adenocarcinoma of sigmoid: a rare case report

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Abstract Colorectal cancer usually present with known symptoms while there are less common manifestation including abscess formation which can be intra or extra peritoneal. A 60-year-old Caucasian male with a history of RLQ abdominal pain, nausea, vomiting and anorexia from 15 days ago referred to surgery ward. Ultrasound showed a hypoachoic lesion with diameters 50 mm × 70 mm in RLQ of abdomen and a round echogenic area in right lobe of liver with diameter 15 mm. The findings were revealed an abscess located in right iliac fossa then local drainage of abscess was performed. Four days later the patient was re-admitted because of severe abdominal distention and lack of bowel movement. Laparoscopy was performed before proceeding with further examinations, due to the poor general condition of the patient. The sigmoid was adherent into the abdominal wall and mild intestinal loop distention and apple-core view was observed during operation. Cancer of sigmoid complicated by a right iliac fossa abscess was diagnosed and Hartman colestomy was undertaken. At the last follow-up examination 3 months after operation, the patient was in good health with no clinical evidence of recurrence.

Key words colorectal cancer; adenocarcinoma; abdominal abscesses

Colorectal cancer usually present with known symptoms such as rectal bleeding, abdominal pain and anemia [1] while there are less common manifestation including abscess formation which can be intra or extra peritoneal. In similar studies abscess formation is reported in 0.3 to 0.4 of colonic carcinoma that is the second most common complication of perforated lesions [2–6] while in a single report perforation is pointed as the most lethal complication of perforated lesions [7]. This report presents a case of abdominal wall abscess secondary to colorectal cancer.

Case report

A 60-year-old Caucasian male with a history of RLQ abdominal pain, nausea, vomiting and anorexia from 15 days ago referred to surgery ward. Past medical history was unremarkable. The patient presented a fever of 38.5 and remarkable tenderness on RLQ of his abdomen. The abdomen was soft and without organomegaly. Thrombocytosis level of 456 000 cell/mm^3 and left-shifted leukocytosis were noted. Total and direct bilirubin and alkaline phosphatase reported higher than normal range. Ultrasound showed a hypoachoic lesion with diameters 50 mm × 70 mm in RLQ of abdomen (Fig. 1) and a round echogenic area in right lobe of liver with diameter 15 mm (Fig. 2). Plain and upright abdomen X-ray was normal. The findings were revealed an abscess located in right iliac fossa then local drainage of abscess was performed. Cultures obtained from the abscess grew *E. coli*. Postoperatively the patient was treated with antibiotics and abscess reduction and was discharged home after 4 days. Four days later the patient was re-admitted because of severe abdominal distention and lack of bowel movement. He was complained of anorexia, weakness, fatigue and he presented decreased stool caliber. He has developed watery and dark diarrhea and stool incontinence at first day of his admission. On examination his sclera was sub icteric. Abdominal examination revealed severe distention, increased bowel sound and RLQ tenderness. Abdominal percussion showed tympan. There were no abnormalities on rectal exam. CBC revealed leukocytosis and thrombocytosis. On plain and upright abdomen X-ray, multiple

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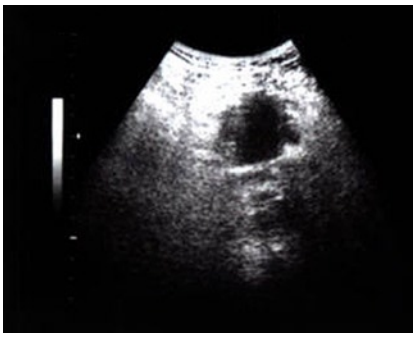

Fig. 1 Ultrasound showing a hypoachoic lesion with diameters 50 × 70 mm in RLQ of abdomen

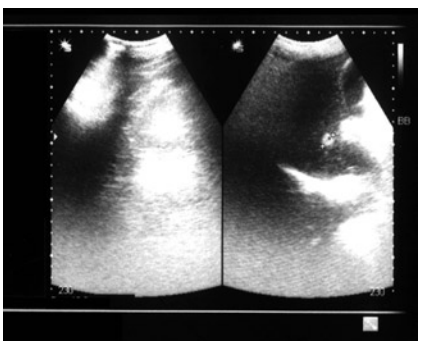

Fig. 2 Ultrasound showing a round echogenic area in right lobe of liver with diameter 15 mm

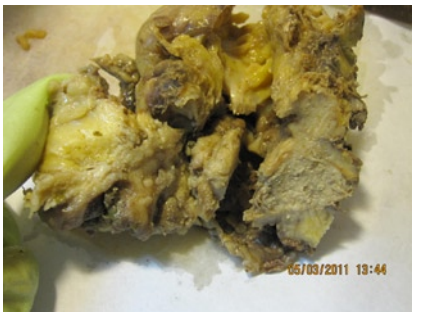

Fig. 3 Macroscopic findings demonstrated a creamy-gray tumor measuring 5 cm in length with no nodal involvement

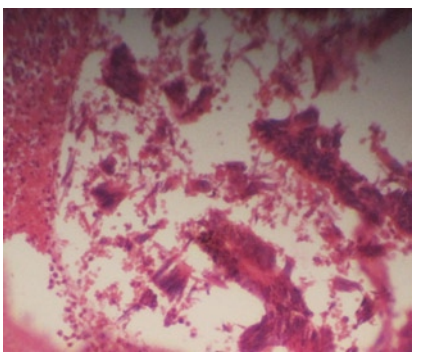

Fig. 4 Pathology revealed a well-differentiated adenocarcinoma of sigmoid

air-fluid level and dilation of intestinal loops were seen. Ascites fluid in lower portion of abdomen was seen. Laparoscopy was performed before proceeding with further examinations, due to the poor general condition of the patient. The sigmoid was adherent in to the abdominal wall and mild intestinal loop distention and apple-core view was observed during operation. Cancer of sigmoid complicated by a right iliac fossa abscess was diagnosed and Hartman colestomy was undertaken. There was no evidence of distant metastasis. Macroscopic findings (Fig. 3) demonstrated a creamy-gray tumor measuring 5 cm in length with no nodal involvement and TNM staging was $T_1N_0M_0$. Tumor distance from one margin was 0.5 cm. Pathology revealed a well-differentiated adenocarcinoma of sigmoid and there was microscopic evidence (Fig. 4) of penetrating tumor through the muscularis propria and stage B_2 in Astler-Coller classification was noted. The patient was discharged after 8 days and he had uneventful post-operative course. At the last follow-up examination 3 months after operation, the patient was in good health with no clinical evidence of recurrence.

Discussion

Colorectal cancers may have invasions to adjoining organs but it is rarely seen as perforation While most of perforation of colorectal cancers in the intra-abdominal cavity Mucinous carcinomas had higher prevalence in colorectal cancers with abdominal abscess [8]. Our case was an adenocarcinoma, a common type of colorectal cancer presenting as right iliac fossa abscess. Some authors have pointed that abscess formation in abdominal wall is a presenting sign of colorectal cancers [9, 10]. However Merrill *et al* [8] reported that only 2.4% of colorectal cancer are associated with anterior involvement. In histologically review Merrill *et al* reported that 36.7% of colon cancers with anterior abdominal wall abscesses were mucinous carcinoma [8] while Rankin [11] believes describes this high prevalence because of slow growing and direct extension spreading of this type of tumors. In conclusion we presented a patient with sigmoid cancer who presented with an abscess in iliac fossa. CT-Scan proved useful for an abscess assessing the statue of tumor, also for patients with anterior abdominal wall abscess due to colorectal cancer a deep excision of the full thickness of anterior abdominal wall including the abscess should be performed [12–14], if this procedure is not possible because of any complication such as large size tumors or wide and extensive abscess, palliative resection of tumor is considerable to save and improve the quality of life of these patients as good as possible.

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Consent

Written informed consent was obtained from patient's relatives for printing this report.

Conflict of interest

The authors declare that they have no conflict of interest.

Author's contribution

MHH interpreted patient's data and was the supervisor of this report. MRM performed the histopathological examination. HRSG was the major contributor to writing this manuscript and FA and BM collected data and collaborated in authors connection. All authors read and approved the final manuscript.

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Adamantinoma of the pelvic bone, a difficult diagnosis with fatal outcome

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Abstract Adamantinoma is a primary low grade malignant bone tumor that is predominantly located in the mid-portion of the tibia. The tumor is of interest for two reasons: first, there still exists considerable dispute as to the origin of the lesion and recent reports reveal that the condition is more malignant than had previously been supposed. Although cases of adamantinoma located to the axial skeleton have been reported, this is the first case of adamantinoma located to pelvic bone in Iran. Here we present the clinical, radiological & histopathological features of a 19 year-old male with painful lesion located to the right pelvic bone which was morphologically and immunohistochemically diagnosed as adamantinoma. In general, metastasis is seen in 15%–20% of patients. The spread can occur to regional nodes, lung and infrequently to skeleton, liver and brain [1]. Several weeks after surgery, our patient's condition gradually worsened. A CT-scan of abdomen revealed widespread liver metastasis and the patient died due to acute liver failure. This case demonstrates that the mortality rate from adamantinoma is not always low.

Key words adamantinoma; pelvic bone; diagnosis

Adamantinoma is a primary, low grade, malignant bone tumor of unknown histogenesis. It is a rare neoplasm comprise only 0.1%–0.5% of all primary bone tumor [2]. The first reported example is attributed to Marier in 1900 [3]. In 1913 Fischer [4] named the lesion "primary adamantinoma of the tibia" because of its striking histologic resemblance to the jaw adamantinoma. In general, adamantinoma is a slow growing tumor and tends to be locally aggressive and rarely metastasizes [5]. The rate of metastasis is approximately 15%–20% and usually occurs in the first two years following diagnosis [6, 7]. The most common sites of metastasis are bone, lung and regional lymph nodes [6]. To our knowledge, until now, adamantinoma has been reported only in few locations in the appendicular skeleton. Here we present a patient with an adamantinoma of the pelvic bone who subsequently developed widespread liver metastasis and died due to acute liver failure.

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Case presentation

A 19 year-old Iranian male complained of pain in the right pelvic area and limping from one year ago. The pain persisted and did not decline over the following several months. There was no history of previous trauma. One month ago he consulted an orthopaedist in the community hospital. According to his medical records, active and passive range of motion of right hip joint were reduced, but neurovascular examination were normal. X-ray and CT scan showed slight sclerosis, cortical thickening, cortical destruction and periosteal reaction (vertical spicules) of right iliac bone with soft tissue thickening of gluteus and iliacus muscles (Fig. 1 and 2). Except for alkaline phosphatase which was 700 U/L (normal value = 80–306 U/L), and all of the laboratory data were unremarkable. Needle biopsy from right anterior iliac bone was performed and a definite pathologic diagnosis could not be made from that specimen, but metastatic adenocarcinoma was considered possibility. Extensive metastasis work up including chest and abdominal CT-scans, Tc-sintigraphy, endoscopy, colonoscopy and tumor markers evaluation were negative. Then the patient referred to our center

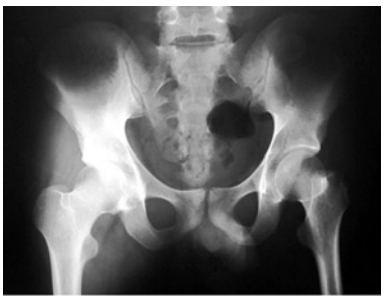

Fig. 1 X-ray showed slight sclerosis, cortical thickening

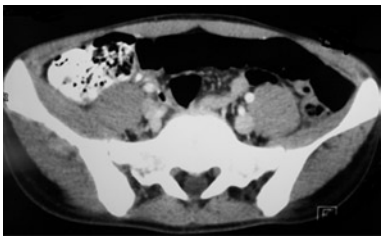

Fig. 2 CT scans showed cortical destruction and periosteal reaction (vertical spicules) of right iliac bone with soft tissue thickening of gluteus and iliacus muscles

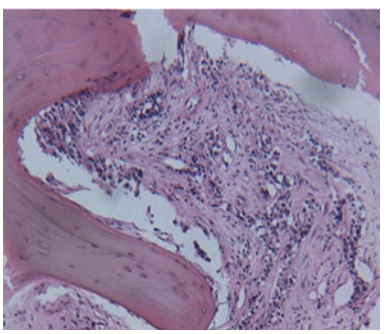

Fig. 3 Microscopic examination showed a biphasic tumor, composed of epithelial and osteofibrous components (× 10)

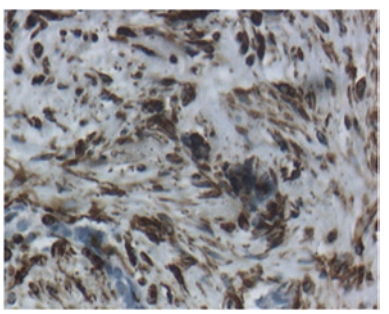

Fig. 4 Epithelial and spindle cells were positive in vimentin staining (× 40)

and underwent open surgery. At surgery, the tumor partly was removed for histologic examination, but a through enucleation was postponded to the next step due to lack of necessary facilities. The resected tissue, which was of hard consistency, paraffin blocks and glass slides related to previous surgery were sent to our department for examination and consultation. Microscopic examination showed a biphasic tumor, composed of epithelial and osteofibrous components. Epithelial cells were medium to large in size with finely dispersed chromatin and an overall bland appearance. Mitotic figures were infrequent. These cells had arranged in nests and tubular or glangular appearance. Islands of epithelial cells were surrounded by spindle cells. The spindle cells had interlacing fascicles and there was no matrix production (Fig. 3). Our diagnosis was classic adamantinoma. IHC studies revealed that the epithelial cells expressed keratins and staining for vimentin was strongly positive in epithelial nests and fibroblast-like stroma (Fig. 4). Tumor cells were negative for S100, CEA and CD99. The diagnosis of adamantinoma was confirmed.

Discussion

This case is of interest because of the lesion located to the pelvic bone and early liver metastasis. Adamantinoma of the long bones is an uncommon, primary low growing malignant bone tumor. Adamantinoma presents a wide variety of histologic type with malignant biologic behavior. Adamantinoma mostly occurs in the second to fifth decade. The mean patient age is 25–35 years with a range from 2 years to 86 years. It is slightly more common in men than women, with a ratio of 5:4 [8]. Our patient was a 19 year-old Iranian male. The tumor has striking predilection for the long bone (97% of cases) and specifically, the tibia (80%–85% of cases). Other bones that are involved in order of decreasing frequency including humorous [9], ulna [10], femur [11], fibula [12], radius [13], innominate bone [14, 15], rib [16], spine [17] and rarely small bones of the hand and foot [18]. The present case is unique in that the patient had a novel site of appearance of adamantinoma. A history of significant trauma has been noted in about 60% of 200 cases reviewed by Moon and Mori [8]. The presented patient had no history of trauma. The initial symptom are often indolent and non specific. Our case complained of pain in the right pelvic area for one year ago. As far as radiologic features are concerned, the most common appearance is that of multiple sharply circumscribed lucent zones of various size, with sclerotic bone interspersed between the zones and extend above and below the lucent zone. Sometimes the radiographic accepts of adamantinoma are similar to the those of osteofibrous dysplasia of tibia [19]. MRI is useful in differentiating between adamantinoma from osteofibrous dysplasia. On plain radiograph, both of them may show polycyclic osteolysis refereed to as soap-bubble appearance. MRI can give information not only on the extend of the tu-

mor, but also about its origin [20]. In the presented case CT scan showed slight sclerosis, cortical thickening, cortical destruction and periosteal reaction (vertical spicules) of right iliac bone with soft tissue thickening of gluteus and iliacus muscles. The main differential diagnosis of adamantinoma is epithelial metastatic neoplasm. However the bland cytological growth along with the soap-bubble like appearance of adamantinoma would be quite unusual for a metastatic epithelial neoplasm. The presented patient underwent extensive metastases work-up which were negative. Adamantinoma are usually treated by excision with wide surgical resection of the tumor and insertion of a segment of intercalary bone allograft or osteoarticular segment [21–23]. Amputation is the treatment of choice in patients presenting with local recurrence, metastases or failure of reconstruction [23]. The tumor appears relatively insensitive to radiotherapy [6] and although the optimal treatment is still controversial, a need for early aggressive surgical treatment has been suggested by some authors [24]. Our patient died before radical surgery. Some studies reported the long term outcome of adamantinoma [25–28]. Male sex, pain, symptoms of < 5 years' duration and initial treatment by biopsy, curettage or resection are risk factors for recurrent or metastatic disease [26]. The rate of distant metastasis in long bone adamantinoma is about 15%–20% [8, 26]. This percentage may be higher because the indolent course of the disease. In 1986 Moon and Mori found 14 metastases in 109 cases [8]. Distant metastases were mainly found in patients with a history of local recurrence, mostly due to inadequate initial treatment. Lungs are most frequently affected, less frequently metastases are found in regional lymph nodes, liver and bones. Szendroi *et al* [28] published a long term follow-up study of 11 cases of adamantinoma of long bones. The authors reported recurrences in 4 patients 20 and 16 years after initial treatment. One patient died of pulmonary metastasis, 9 years after diagnosis. Although adamantinoma is a low grade, slow growing malignant bone tumor, a lifelong follow-up of the patient is necessary due to the possibility of recurrences or metastasis even decades after the primary tumor. Mortality rates of 13% [26] to 18% [8] have been reported. The mean duration of survival with metastatic adamantinoma of long bones is estimated to be approximately 13 years [29]. To our knowledge liver metastasis in adamantinoma is rare and has favorable course [30] but in contrary the presented case is unique in that the patient had not only a novel site of appearance but also had early widespread and fatal liver metastasis. We find that the mortality rate from adamantinoma is not low and early aggressive treatment and long term follow up are mandatory. Recently, the least common variant of adamantinoma has been described as Ewing's sarcoma like adamantinoma or adamantinoma like Ewing's sarcoma. The cells exhibits features of both epithelial cells and neuroendocrine cells. IHC have shown the tumor cells to contain both epithelial and neural antigens [31, 32]. Bridge *et al* [33] documented translucation (11, 21) in the nuclei of cytokeratin-immunoreactive cells. Identification of t (11, 21) by cytogenetic and/or molecular genetic techniques is specific in Ewing's sarcoma, however is not universally available. So IHC techniques are more popular. In about our case the tumor cells were negative for CD 99 and S100 antigens and the cells did not have "round cell" morphology. The histogenesis of this variant is not clear, however Ewing's sarcoma is considered to be derived from primitive pleuripotential stem cells that may differentiate into cells with mesenchymal, epithelial and neural features. In conclusion the diagnosis of adamantinoma requires knowledge of compatible clinical and radiologic studies as well as understanding of the variable histologic patterns that one may encounter. In addition we find that the mortality rate from adamantinoma is not always low and early aggressive treatment and long term follow up are mandatory.

Conclusion

Adamantinoma of the long bones is an uncommon, primary low growing malignant bone tumor. Although cases of adamantinoma located to the axial skeleton have been reported, but it is rare. The diagnosis of adamantinoma requires knowledge of compatible clinical and radiologic studies as well as understanding of the variable histologic patterns that one may encounter. The mortality rate from adamantinoma is not always low and early aggressive treatment and long term follow up are mandatory.

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Activities Report

Cancer Pain Master Class for China, 2012 was held in Beijing, Guangzhou and Shanghai

Author/Photo: Yi Cheng, from Tongji Cancer Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

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Fig. 1 Professor Bart Jan Morlion made the speech

From May 16th–18th, Cancer Pain Master Class for China, 2012, hosted by Mundipharma (China) Pharmaceutical Co., Ltd., was held in Beijing, Guangzhou and Shanghai. More than 1200 oncological medical staff took part in the activities.

The activities invited Professor Bart Jan Morlion, the chief of the Leuven Centre for Pain Management and president of the Belgian Pain Society, IASP. He presented an excellent speech titled as "considerations in opioid titration in cancer pain". In the speech he focused on epidemiology and aetiology of cancer pain, transition from acute to chronic pain, pharmacotherapy of cancer pain, principles of opioid titration and choice of opioid. He emphasized the balance between pain alleviation and the side effects when patients took opioid drugs, and the recommendation for breakthrough pain, nausea, vomiting and dizziness. In his hospital both of titration methods were carried on: short-acting opioid drugs only and a combination of long-acting opioid drugs and short-acting opioid drugs. The latter method should be recommended, since it simplified the treatment, reduced the risk of low compliance and thereby enhanced efficacy.

Fig. 2 The conference in Guangzhou

The "Cancer Pain Master Class for China, 2012" activities aimed to elevate the acknowledge of cancer pain among medical staff, and they matched up with "Good Pain Management Ward" national selection hosted by Ministry of Public Health in this year. It was reported that the selection would be launched in June.

Contribution Invitation of Chinese-German Journal of Clinical Oncology

Chinese-German Journal of Clinical Oncology is an international professional academic periodical on oncology, being co-edited by China and Germany. The Journal, with the authors from around world, especially from China, is dominated in introducing the clinical experience of diagnosis and treatment as well as leading scientific research achievement in the tumor domain, in addition to report basic theory researches which help instruct the clinical practice of oncology and closely connect with the discipline. All the manuscripts are published in English, monthly issued both internal and external, 64 pages, 16 opens domains, art paper in offset printing, with lay-out by international customs, unified issuing number: ISSN 1610-1979 (Paper) 1613-9089 (Online) /CN 42-1654/R.

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Manuscripts must be submitted by one of the authors of the manuscript, and should not be submitted by anyone on their behalf. The submitting author takes responsibility for the article during submission and peer review. Manuscripts should be scientific, advanced, pragmatic, concise, clear, well-arranged, well-informed and data-accurate. Provided the manuscript is to be printed, full text will be published in English. To facilitate rapid publication and to minimize administrative costs, *Chinese-German Journal of Clinical Oncology accepts online submission, website: www.editorialmanager.com/tcgj.*

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T*itle page*: It contains the title of the article, which should be concise but informative. The names of all authors are to be placed under the title in sequence, and personal signatures in the same sequence are a must. Pay attention to accuracy of the title, the names of all authors with their affiliations and the contacting methods in English (address, postcode, telephone and fax number, Email address, etc.).

A*bstract and key words:* A structural abstract of no more than 250 words is to be put on the second page. It should embody four parts, objectives, methods, results and conclusion. It's desirable to employ the third person to write, not "this article" or "the author" in stead of. Supply three to eight key words or short phrases, and terms from the medical subject heading (MeSH) list Index Medicus should be adopted, each word being separated by semicolon.

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1 Bold RJ, Ota DM, Ajani JA, *et al*. Peritoneal and serum

tumor markers predict recurrence and survival of patients with respectable gastric cancer. Gastric Cancer, 1999, 2: 1–7.

2 Weinstein L, Swartz MN. Pathologic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. 8th ed. Philadelphia: Saunders, 1974. 457–472.

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