Clinical Studies of Postoperative Arterial Infusion Chemotherapy in Patients with Pathologic T_3 Esophageal Squamous Carcinoma

Baodong Liu
Zongjun Dong
Xiuyi Zhi
Qingsheng Xu

Department of Thoracic Surgery, Xuanwu Hospital of Capital University of Medical Sciences, Beijing 100053,China.

Correspondence to: Baodong Liu
Tel: 86-10-63013355 ext.8646
E-mail:ryouhoutou@yahoo.com.cn

Received January 12, 2006; accepted May 22, 2006.

OBJECTIVE To evaluate how arterial infusion chemotherapy after radical surgery influences long-term survival of patients with pathologic T_3 (pT_3) esophageal squamous carcinoma.

METHODS We divided 190 patients with pathologic pT_3 esophageal squamous carcinoma, confirmed by consecutive radical surgery, into an experimental group (surgery + intra-arterial infusion, 56 $T_3N_0M_0$ and 52 $T_3N_1M_0$ cases), and the remaining patients into a control group (surgery alone, 48 $T_3N_0M_0$ and 34 $T_3N_1M_0$ cases). The experimental group was sub-grouped into 56 cases (26 $T_3N_0M_0$ and 30 $T_3N_1M_0$ cases) receiving 1 or 2 periods of chemotherapy, while 52 cases (30 $T_3N_0M_0$ and 22 $T_3N_1M_0$ cases) underwent 3 or more than 3 periods of chemotherapy. We used one to seven courses of selected arterial infusion chemotherapy of cisplatin (80 mg/m^2 of body-surface area) and fluorouracil (800 mg/m^2) with or without epirubicin at 3~4 weeks post operation. The interval between each period was 3~4 weeks. All cases were followed-up for more than 5 years. Survival rates were calculated by the Kaplan-Meier methods and survival differences between patients with and without selected arterial infusion chemotherapy were compared with the Log-rank test. Prognostic variables were entered into a Cox regression analysis model controlling for age, site, lymph node status, and treatment received.

RESULTS The overall survival rates were not significantly different between the experimental group and the control group, but there was better survival for patients who received 3 or more than 3 courses of chemotherapy. Lymph node status (N) was an important factor in the prognosis.

CONCLUSION Trans-catheter arterial infusion chemotherapy is a safe and effective method of therapy. Postoperative selective arterial infusion chemotherapy can improve the survival rate in patients with esophageal squamous carcinoma who were previously treated by radical surgery. However, this modality of therapy needs further investigation.

KEYWORDS: esophageal squamous carcinoma, arterial infusion, chemotherapy.

Multi-sample and multi-center studies have provided no evidence to indicate that preoperative chemo-radiation therapy can increase the 5 year survival rate of patients with esophageal squamous carcinoma, although some clinical studies have indicated that preoperative chemotherapy is effective. It is known that adjuvant chemotherapy after an operation can decrease the micro-metastases, but there have been few investigations as to whether it can increase the long-term survival rate, especially by use of arterial infusion chemotherapy. This research was designed to evaluate if arterial infusion chemotherapy influences long-term survival in pT_3 esophageal squamous carci-

万方数据

noma patients after radical surgery.

MATERIALS AND METHODS

This study involved 190 patients with pT_3 esophageal squamous carcinoma, from January 1990 to January 1999, who were treated with radical surgery. Their ages were 40~81 with a mean of 63 years, and were comprised of 158 males and 32 females. Their Karnofsky scores were over 70~80.

We adopted the AJCC-UICC 1997 stage classification to divide patients into an experimental group (108 cases, including 56 $T_3N_0M_0$ and 52 $T_3N_1M_0$ cases) and a control group (82 cases, including 48 $T_3N_0M_0$ and 34 $T_3N_1M_0$ cases). In addition the patients were further divided into 2 groups based on the number of chemotherapy treatments received. One group of 56 cases was treated 1or 2 times (26 $T_3N_0M_0$ and 30 $T_3N_1M_0$ cases) and a second group of 52 cases received 3 or more treatments (30 $T_3N_0M_0$ and 22 $T_3N_1M_0$ cases). The Seldinger technique was used to insert a catheter into the celiac trunk artery. Routine DSA was employed, using compound meglumine diatrizoate. The 40%~50% of a dose of 10 ml and flow velocity of 5 ml/s (cisplatin 40 mg and fluorouracil 1 g) was diluted into 40~50 ml of saline and injected intra-arterially over 15 min. The catheter was immediately removed after administration of the drugs, the puncture was pressed for 15~20 min, and bandaged with pressure for 12~24 h. Limb movement was restricted for 6~8 h, and like with venous chemotherapy, the patients were monitored for back pain, and limb numbness. Routine blood tests and kidney and hepatic function were assessed 1 week after operations, and again every 4~6 weeks. After 2~3 determinations the efficacy of the therapy was evaluated. Statistics: SPSS10.0 software was utilized, and the Kaplan-Meier survival analysis (Log-rank test), and the COX proportion risk model used to evaluate the important factors effecting prognosis.

RESULTS

Because there is no specific marker to determine the effectiveness of radical treatment of esophageal squamous carcinoma, only long-term follow-up of the survival rate can be used to determine the efficacy of the arterial infusion chemotherapy. As to our study, there was no statistically significant difference between the mean survival time of the two groups (Table 1). The results were the same even when the cases were divided into the presence or absence of lymphatic metastasis (Tables 2,3).

Comparison of survival times between patients receiving chemotherapy 3 times or more than 3 courses versus those treated less than 3 times showed a significant difference (Table 4, Fig.1). When the same analysis was conducted discounting lymphatic metastasis, the results showed that the number of chemotherapy treatments did not effect the long-term survival rate (Tables 5, 6).

Cox proportion risk model analysis, Wald=8.510, P=0.004, showed that N is the key factor effecting the prognosis of esophageal squamous carcinoma (Table 7, Fig.2).

Side effects: no severe complications occurred but only low fever, nausea and upper abdominal discomfort. No treatment was needed and all the symptoms disappeared after 2~3 days.

DISCUSSION

Esophageal squamous carcinoma is still a common tumor in China, although its mortality and incidence rates recently have decreased.[1] The pathologic classification in Asia is mainly squamous carcinoma, while in Western countries, adenocarcinoma has greatly increased accounting for 40~50% of the cases.[2-4] Excision has long been recommended as the best mode of treatment.

It is estimated that 70%~80% of the patients have no chance of having an operation. Because of the special anatomical location of the esophagus, it is difficult to detect the tumor early except in areas where there is a high incidence. Although operation techniques have improved greatly, the long-term survival rate needs to be improved.

The five-year survival rate for patients with esophageal squamous carcinoma is lower than 10% at present, and even for those cases which are considered to be curable, the five-year survival rate is only around 20%~30%. Squamous carcinoma should be considered to be a systemic disease, whether or not there are early lymphatic metastases. Furthermore, it is a multicenter disease, and early squamous carcinoma has unlocalized pathological changes, so the general treatment is useful for the middle and late stages of esophageal squamous carcinoma.

The usual treatment of a combined operation and systemic chemotherapy, often produces unsatisfactory results for the following reasons. Patients suffer from chemotherapeutic side effects, the tumor may have

万方数据

Table 1. Survival analysis between the experimental and control groups

Groups	Cases	Mean survival time (months)
Experimental	108	29 ± 3
Control	82	29 ± 4

Log-Rank=0.5170

There was no statistical difference between the 2 groups.

Table 2. Survival analysis of $T_3N_1M_0$ cases between the experimental and control groups

Groups	Cases	Mean survival time (months)
Experimental	52	23 ± 4
Control	34	17 ± 3

Log-Rank=0.3797

Table 3. Survival analysis of $T_3N_0M_0$ cases between the experimental and control groups

Groups	Cases	Mean survival time (months)
Experimental	56	34 ± 4
Control	48	36 ± 6

Log-Rank=0.8691

Using delamination analysis to evaluate whether there was lymphatic metastasis, showed there is no significant difference between the mean survival time of the 2 groups.

Table 4. The mean survival time based on the chemotherapy times of treatment

Treatment number	Cases	Mean survival time (months)
1 or 2	56	24 ± 4
3 or >3	52	34 ± 4

Log-Rank=0.0455

Table 5. The mean survival time for the chemotherapy times in $T_3N_0M_0$

Treatment number	Cases	Mean survival time (months)
1 or 2	26	27 ± 6
3 or >3	30	42 ± 6

ULog-Rank=0.1080

Table 6. The mean survival time based on the chemotherapy times of treatment in $T_3N_1M_0$ cases

Treatment number	Cases	Mean survival time (months)
1 or 2	30	20 ± 5
3 or >3	22	26 ± 3

There was a significant difference between the mean survival time for patients receiving chemotherapy over 3 times or 3 times or less than 3 times based on analysis separating chemotherapy treatment. But when the same analysis was conducted without lymphatic metastases, it showed that the number of chemotherapy treatments did not effect the long-term survival rate.

Table 7. Mean survival time based on the N in esophageal squamous carcinoma

N	Cases	Mean survival time (months)
$T_3N_0M_0$	104	38 ± 4
$T_3N_1M_0$	86	21 ± 3

Log-Rank=0.0024

Cox proportion risk model analysis, Wald=8.510, P=0.004, which showed that N is the key factor effecting the prognosis of esophagus squamous carcinoma patients (Table 7, Fig.2).

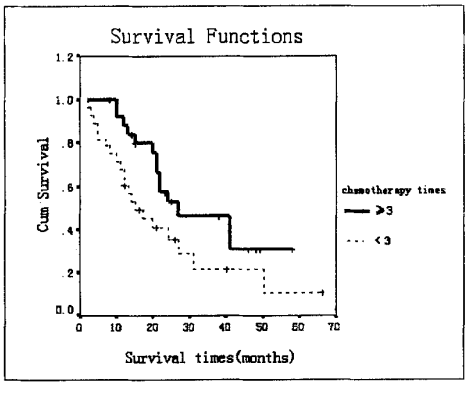

Fig.1. Long-term survival was influences by the number of chemotherapy treatments in pT_3 esophageal squamous carcinoma patients after radical surgery.

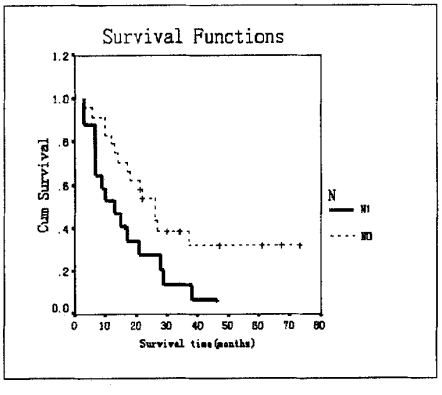

Fig.2. Long-term survival was influenced by lymph node status (N) in pT_3 esophageal squamous carcinoma patients after radical surgery.

万方数据

poor circulation so the drug level can not reach a therapeutic concentration, and only a portion of the cancer cells are in a proliferative stage. Some investigations have shown that neajuvant chemotherapy can increase the excision rate, but studies of the total survival rate with multi-centers, and a large cohort are needed.[5-8]

The effect of chemotherapy is not only related to the sensitivity of the tumor to the pharmacological action of the drug, but also proportional to the drug concentration and the time it is in contact with the tumor.[9-11] Accordingly, selective arterial infusion chemotherapy can increase the efficacy of treatment, and lessen the side effects caused with venous chemotherapy by increasing the drug concentration at the target organ, and by lengthening the contact time with the drugs. Thus in the early 1950's, Klopp tried to inject anti-tumor drugs through the arteries that supply blood for the tumor. Up to now hepatic arterial infusion chemotherapy for treating liver cancer has been widely used. In 1975, Tanohata first used angiography combined with arterial infusion chemotherapy to treat esophageal squamous carcinoma. Intravascular intervention has now become a new branch of clinical medicine.

Indications for esophageal squamous carcinoma arterial infusion chemotherapy are now unclear but may include the following: 1) if there are no metastases, localized in the artery supplying the esophageal segment. 2) for thorax esophageal squamous carcinoma which has invaded the surrounding organs, operation after chemotherapy is recommended. 3) if the tumor has vascular supply which is confirmed by angiography.

Contraindications include main organ dysfunction, valetudinarianism, coagulation dysfunctions, infection, fever, perforation and bleeding.

Complications include thrombosis, haematoma, infection, esophageal ulcer bleeding and so on. Among the complications, spinal cord injury is the most serious. The reasons may be:1) the toxicity of ion-type contrast agents. 2) 90% of the blood supply to the spinal cord comes via the intercostal arteries (segmental arteries) which have few anastomoses, therefore, the left 5th intercostal arteries spasm resulting in spinal cord injury due to lack of a blood supply. 3) the catheter may obstruct the blood supply or cause vascular thrombosis. 4) the toxicity of the anti-tumor drugs.

Lower limb movements and sensations and so on should be observed in order to prevent spinal injury. It is quite important to be familiar with the anatomy of the blood supply for the target area as complex anastomoses and variance of the vascular supply makes arterial infusion chemotherapy difficult.

Studies of arterial infusion chemotherapy in China have indicated that the short-term effective rate is around 50%, suggesting that this procedure is mainly for late-stage patients who are beyond receiving an operation. Our study showed that there was no significant difference between arterial infusion chemotherapy at pT3 postoperation compared to those in the late pT3 esophageal squamous carcinoma, but it can prolong the survival time.

COX proportion risk model analysis (Wald=8.510, P=0.004), showed that N was the key factor influencing prognosis. Our study indicated that the long-term survival rate was improved when 3 or more than 3 courses of arterial infusion chemotherapy were administered compared to fewer treatments.

Arterial-perfusion chemotherapy does not have a superiority over systemic chemotherapy treatment of tumors, which may be related to with the fact that the chemotherapeutics are unable to enter the tumor bed because of intraoperative ligation of the artery supplying the tumor tissue, and the level of drugs cannot be increased by collateral circulation. At present it is not clear if there is a benefit with postoperative arterial-perfusion chemotherapy, however, local recurrence or liver metastasis in this study was much less compared to the controls.[12]

A multi-center study with a large number of patients is needed, including the choice and combination of drugs. With the development of new drugs (paclitaxel, CPT11, Gemzar), production of new chemotherapeutic regimens, and molecular target treatment (Iressa), [13,14] the efficacy of arterial infusion chemotherapy can be improved in the future.

REFERENCES

1 Wang LD, Yang HH, Fan ZM, et al. Cytological screening and 15 years' follow-up (1986–2001) for early esophageal squamous cell carcinoma and precancerous lesions in a high-risk population in Anyang County, Henan Province, Northern China. Cancer Detect Prev 2005;29:317–322.

2 Lepage C, Bouvier AM, Manfredi S, et al. Trends in incidence and management of esophageal adenocarcinoma in a well-defined population. Gastroenterol Clin Biol 2005; 29:1258–1263.

3 DeMeester SR. Adenocarcinoma of the esophagus and cardia: a review of the disease and its treatment. Ann Surg Oncol 2006;13:12–30.

4 Pera M, Manterola C, Vidal O, et al. Epidemiology of esophageal adenocarcinoma. J Surg Oncol 2005;92:151–159.

5 Kelsen DP, Ginsberg R, Qian C, et al. Chemotherapy followed by operation versus operation in the treatment of patients with localized esophageal cancer: a preliminary

万方数据

report of intergroup study 113 (RTOG89-11). Proc Am Soc Clin 1997;16:276a(abstract #982).
6 Urschel JD, Vasan H, Blewett CJ. A meta-analysis of randomized controlled trials that compared neoadjuvant chemotherapy and surgery to alone for resectable esophageal cancer. Am J Surg 2002;183:274-279.
7 Kelsen DP. Multimodality therapy of local regional esophageal cancer. Semin Oncol 2005;32 (6 Suppl 9):S6-10.
8 Nabeya Y, Ochiai T, Matsubara H, et al. Neoadjuvant chemoradiotherapy followed by esophagectomy for initially resectable squamous cell carcinoma of the esophagus with multiple lymph node metastasis. Dis Esophagus 2005;18:388-397.
9 Bedard EL, Inculet RI, Malthaner RA, et al. The role of surgery and postoperative chemo radiation therapy in patients with lymph node positive esophageal carcinoma. Cancer 2001;91:2423-2430.
10 Ando N, Iizuka T, Ide H, et al. Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus: A Japan clinical oncology group study -JCOG9204. J Clin Oncol 2003;21: 4592-4596.
11 Rice TW, Adelstein DJ, Chidel MA, et al. Benefit of postoperative adjuvant chemo radiotherapy in loco regionally advanced esophageal squamous carcinoma. J Thorac Cardiovasc Surg 2003;126:1590-1596.
12 Lee J, Lee KE, Im YH, et al. Adjuvant chemotherapy with 5-fluorouracil and cisplatin in lymph node-positive thoracic esophageal squamous cell carcinoma. Ann Thorac Surg 2005;80:1170-1175.
13 Williamson SK, McCoy SA, Gandara DR,et al. Phase II trial of gemcitabine plus irinotecan in patients with esophageal cancer: a Southwest Oncology Group (SWOG) trial. Am J Clin Oncol 2006;29:116-122.
14 Sutter AP, Hopfner M, Huether A, et al. Targeting the epidermal growth factor receptor by erlotinib (Tarceva) for the treatment of esophageal cancer. Int J Cancer. 2006; 118:1814-1122.

CONT from p175

6 Li SL. Oncology of Breast (Chinese). Beijing:People's Medical Publishing House. 2000;4.
7 Liebert A, Quietzsch D, Beier L. Comparison of the tumor associated proteases cathepsin D (CATH D) and urokinase-type plasminogen activator (uPA) in cytosols of human breast cancer patients. Anticancer Res. 1999;19: 2571-2576.
8 Dittadi R, Biganzoli E, Boracchi P, et al. Impact of steroid receptors, pS2 and cathepsin D on the outcome of N+ postmenopausal breast cancer patients treated with tamoxifen. Int J Biol Markers. 1998;13:30-41.
9 Pujol P, Daures JP, Brouillet JP, et al. Time at surgery during menstrual cycle and menopause affects pS2 but not cathepsin D levels in breast cancer. Br J Cancer. 1999;79: 909-914.
10 Athanassiadou P, Sakellariou V, Michalas S, et al. Immunocytochemical localization of Cathepsin D and CA 125 in ovarian cancer. Int J Gynaecol Obstet. 1997;56:31-37.

万方数据