

Brief Reports

Intensify standardized therapy for esophageal and stomach cancer in tumor hospitals

Shi Jie Wang, Deng Gui Wen, Jing Zhang, Xin Man and Hui Liu

Subject headings esophageal neoplasms/therapy; stomach neoplasms/therapy; endoscopy, digestive system; chemotherapy, adjuvant; radiotherapy; surgery, operative

Wang SJ, Wen DG, Zhang J, Man X, Liu H. Intensify standardized therapy for esophageal and stomach cancer in tumor hospitals. *World J Gastroenterol*, 2001;7(1):80-82

INTRODUCTION

Cancer treatment situation in tumor hospitals in China has its own unique characteristics which are not found in other parts of the world. Because of the huge population and high incidence rates of esophageal and stomach cancer^[1-5], the number of cancer patients waiting for admission is inconceivably large. It is estimated that there are about 1.6-2.0 million new cases per year in China. In 1999, the Hebei Tumor Hospital had 6884 carcinoma patients hospitalized, among them there were 1035 esophageal cancer and 1057 stomach cancer patients. Because of the financial problem and most peasants have not joined the medical care insurance plan. Therefore, they are not benefited by the ideal treatment regimen after being diagnosed with TNM staging.

Hebei Tumor Hospital was established in 1958 to provide medical care to cancer patients in the central and southern parts of Hebei Province. It has 621 beds. The southern part of Hebei Province around Chixian is adjacent to Linxian of Henan Province, both Chixian and Linxian counties have the highest incidence rates of esophageal cancer which are 135/100 000. Besides, stomach carcinoma is another major cancer in this region.

With a view to standardize the therapy of esophagus and stomach cancer, the authors reviewed the national and international standard treatment and recent progress in this field, and the therapeutic modalities given in this hospital from 1981 to 1997, and hope this analysis may benefit the development of standardized therapy for the

above two malignances in clinical management.

MATERIALS AND METHODS

A database was constructed for esophageal and stomach cancer patients who had been hospitalized in Hebei Tumor Hospital from 1981 to 1997 by the Foxprow database management techniques. Each hospitalized patient had his or her own record in the dataset. Percentages of therapeutic modalities as surgery, radiotherapy, chemotherapy, separate or in combination were calculated by the programs written in the Foxprow language. Finally, the results were analyzed according to *Diagnosis and Treatment Criteria for Common Malignances in China* by Ministry of Health of China and *Manual of Clinical Oncology* by UICC, and recent advances in these fields so as to find out the most rational suggestions for esophageal and gastric cancer.

RESULTS AND DISCUSSION

Esophageal carcinoma

As seen in Table 1, surgery and radiotherapy are two major options for esophageal cancer. Only 2.76% of the patients were treated by chemotherapy alone, and even fewer cases had been treated by multimodality treatment regimens such as surgery + radiotherapy, surgery + chemotherapy, chemoradiotherapy, and surgery + chemoradio-therapy. Radiotherapy as a preoperative option is eligible for esophageal cancer of various locations^[6]. Preor postoperative radiotherapy in addition to surgery could reduce tumor recurrence and metastasis^[7,8]. Either surgery or radiotherapy alone is not satisfactory because of the high rate of recurrence and metastasis^[9,10]. The rationale for preoperative radiotherapy includes cytoreduction, improved resectability and reduced chance of marginal dissemination of tumor during the surgical procedure^[11]. Therefore, preoperative radiotherapy is especially beneficial to patients with middle or late stage esophageal cancer^[12].

Postoperative radiotherapy had been proved to be useful in reducing recurrence and metastasis^[11]. Recent trials showed that although the 5-year survival rate of esophageal cancer was still poor, it had improved somewhat from 3% 30 years ago to 10%-15% today^[13]. It was reported that multimodality approaches combining surgery, radiotherapy, and chemotherapy had resulted in 5-year survival rate of 40%-75% for advanced stage patients with a complete histological response to

Dr. Shi Jie Wang, graduated from Hebei Medical University in 1973, Professor of Cancer Surgery, President of Hebei Tumor Hospital (Fourth Affiliated Hospital of Hebei Medical University) and Hebei Cancer Institute, having 27 papers published.

Supported by the Hebei Provincial Scientific Commission, No. 97276162D

Correspondence to: Dr. Shi Jie Wang, Hebei Tumor Hospital, 5 Jiankanglu, Shijiazhuang 050011, Hebei Province, China

Received 2000-07-12 **Accepted** 2000-07-26

preoperative chemotherapy^[14]. These results suggest that further improvement in multimodality treatment regimens may allow a significant increase in survival period for esophageal carcinoma patients in the future^[15].

Preoperative chemotherapy has been shown in nonrandomized trials to have similar side effects and mortality rate with surgery alone. Furthermore, phase two trials have suggested higher survival rates for combination of preoperative chemotherapy and surgery than that seen in surgery alone^[16]. Another randomized study of 113 patients with esophageal carcinoma found that preoperative Cisplatin and 5-Fu given concurrently with 40 Gy of radiation significantly improved 3-year survival rate (32% vs 6%)^[17]. Criticism of the study included poor preoperative staging and small sample size (113 patients). However, this trial offered hope that multimodality treatment regimens may ultimately prove beneficial in improving the overall survival period in esophageal cancer.

As seen in Table 1, although the cured and improved rate on discharge was highest in patients treated by surgery + radiotherapy, the percentage was only 3.58%, far less than those with surgery alone (48.93%) or radiotherapy alone (32.87%). The percentage of multimodality treatment regimens was only 4.32%, this was because in the past, we adopted the policy of elimination of symptoms rather than eradication of the disease. Therefore, in the future, we should focus our attention on the multimodality treatment regimens and to search for the most eligible combinations.

Table 1 Treatment modalities of esophageal and stomach cancer patients from 1981 to 1997 in Hebei Tumor Hospital

Treatment modality	Esophageal cancer			Stomach cancer		
	n	%	Cured & improved(%)	n	%	Cured & improved(%)
Surgery	4683	48.93	92.70	5328	67.48	59.51
Radiotherapy	3146	32.87	93.01	1758	22.26	56.66
Chemotherapy	264	2.76	91.67	117	1.48	84.67
Surgery+radiotherapy	343	3.58	95.04	260	3.29	93.83
Surgery+chemotherapy	41	0.43		114	1.44	88.60
Chemo-radiotherapy	24	0.25	87.50	8		87.50
Surgery+radio+chemotherapy	5			4		75.00
Other therapy	1064	11.12	53.20	307	3.89	83.71
Total	9570	100.00	88.46	7896	100.00	84.04

Gastric carcinoma

As seen in Table 1, surgery remains the first choice as curative treatment for patients with gastric cancer, especially at the early stages^[18-20]. Early intraepithelial gastric cancer without nodal metastasis by surgery alone can yield a 5-year survival rate as high as 90%-95%. These early carcinomas may also be treated by endoscopic resection or endoscopic mucosectomy^[21-24]. Gastric cancer survival is clearly stage dependent and is significantly affected by lymph node involvement^[25]. The 5-year survival rate for patients with early gastric carcinoma after treatment

approaches 90% but only less than 5% for cancer that involves the serosa^[26]. The better survival statistics among Japanese are mainly due to greater frequency of early gastric cancer. Early detection of gastric carcinoma relies upon advanced development of X-ray and endoscopies^[27,28], and also upon massive screening in high risk populations.

Although surgery has been proven to be the curative therapy for early gastric cancer, unfortunately, only 10% are early cancers^[29]. In fact, locoregional recurrence is also common even after curative resection^[30,31], therefore adjuvant chemo and radiotherapies are absolutely necessary^[32-34].

Currently, preoperative chemotherapy and intraoperative radiotherapy are used as adjuvant therapies.

The operative morbidity of gastrectomy is high. It frequently precludes patients from entering into adjuvant therapy in a timely manner. Therefore, many studies are investigating the use of preoperative therapy. Wilke *et al*^[35] described 34 patients who were demonstrated at laparotomy to have locally advanced unresectable cancer, these patients received two to five cycles of etoposide, doxorubicin, and cisplatin (EAP), 70% responders were offered a second laparotomy, and 15 were without clinical evidence of local extension. Kelsen *et al*^[36] reported 56 patients who underwent preoperative therapy with FAMTX combined with postoperative intraperitoneal 5-FU and Cisplatin, among whom 34 patients received a potentially curative resection. For the entire group, the median survival period was 15 months; however, for those who underwent the above preoperation chemotherapy and surgical resection, the median survival period was 31 months. Lowy *et al*^[37] reported 24 patients who responded to similar therapy, 84% had a 5-year disease-free survival, while 30% of those who did not respond had a 5-year disease-free survival. These studies suggest an appealing potential benefit of preoperative chemotherapy by inducing positive response in some patients^[38].

The largest experience with intraoperative radiotherapy (IORT) came from Japan, where it had been studied for over 20 years. Abe *et al*^[39] performed a prospective randomized trial of IORT in over 200 gastric cancer patients, and a more significant survival advantage was found for patients treated with IORT and surgery over those treated by surgery alone. This 5-year survival advantage was seen in patients with stage two (84% vs 62%) and stage three (62% vs 37%). Patients with stage one disease received no benefit from IORT. In addition, the only 5-year survivors in stage four were those who received IORT. This study suggests that IORT may be able to control locoregional recurrence after resection, which alone is often a major cause of treatment failure.

According to the criteria for gastric cancer

therapy modality planning of the Diagnosis and Treatment Criteria for Common Malignancies in China for early gastric carcinomas with no nodal metastasis, no adjuvant therapy is necessary following curative resection depending on whether the disease is restricted to the mucosa or submucosa, but if there is nodal metastasis, adjuvant chemotherapy should be considered. For stage two and/or stage three progressive gastric cancer patients, preoperative radiotherapy is helpful to improve resectability. Postoperative chemotherapy should be considered for all progressive gastric cancer patients whether they have undergone curative or noncurative resection, and whether there is nodal metastasis or not. Intraoperative radiotherapy should be applied for stage two or stage three patients who are undergoing curative resection^[40].

As seen in Table 1, the percent of surgery alone for treatment of gastric cancer is 67.48%, surgery plus chemotherapy and surgery plus radiotherapy account for only 1.44% and 3.29% respectively. Considering only 10% of gastric cancer patients diagnosed in hospitals are early cancer and may be treated by surgery alone, all other patients present with advanced disease should be treated by multimodality regimens such as preoperative chemotherapy, pre, intra or postoperative radiotherapy etc.

CONCLUSIONS

The advent of multimodality treatment is introduced in the last decade. Pre-operational chemotherapy can eliminate micro-metastasis and post-operational radiotherapy can kill the residual cancer cells, therefore in the future surgical resection with preoperational chemotherapy and postoperational radiotherapy should be considered to achieve better results and longer-survival periods.

REFERENCES

- Zhou Q, Wang LD, Gao SS, Li YX, Zhao X, Wang LX. p53 immunostaining positive cells correlated positively with S phase cells as measured by BrdU in the esophageal precancerous lesions from the subjects at high incidence area for esophageal cancer in northern China. *World J Gastroenterol*, 1998; 4(Suppl 2):106-107
- Zhang XY. Some recent works on diagnosis and treatment of gastric cancer. *World J Gastroentero*, 1999;5:1-3
- Yuan Y, Gong W, Xu RT, Wang XJ, Gao H, Dong M, Wu HQ, Wang L, Wang MX, Song XJ, Wang FC, Jiang H, Song LY, Li X, Zhou BS, Zhang YC. A gastric cancer surveillance on 50 000 natural inhabitants of 16 villages and towns in Zhanghe China. *Huaren Xiaohua Zazhi*, 1998;6 (Suppl 7):478
- Cai L, Yu SZ. A molecular epidemiologic study on gastric cancer in Changde, Fujian Province. *Shijie Huaren Xiaohua Zazhi*, 1999;7:652-655
- Zhong YR, Ye TS. Incidence distribution of gastric, cardiac, and esophageal cancer of 1 436 cases. *Huaren Xiaohua Zazhi*, 1998;6(Suppl 7):445
- Sherman Jr CD. Digestive carcinomas. In: Union Internationale Contre Le Cancer (UICC). Manual of clinical oncology 5. Beijing: The joint publishing house of Beijing Medical University and China. *Saint Medical University*, 1992:37-38
- Chen KN, Xu GW. Diagnosis and treatment of esophageal cancer. *Shijie Huaren Xiaohua Zazhi*, 2000;8:196-202
- Chen DF. Outside-radiotherapy in combination with intra-radiotherapy in the treatment of 121 cases of esophageal cancer. *Huaren Xiaohua Zazhi*, 1998;6:127
- China Ministry Of Health. Esophageal cancer. In: China Ministry Of Health, ed. *Diagnosis and treatment criteria for common malignancies in China 2*. Beijing: The joint publishing house of Beijing Medical University and China Saint Medical University, 1991:30-31
- Zou HY, Huang GD, Liu JH, Wang M, Zheng GJ. Radiotherapy in the treatment of above-collarbone nodal metastasis in 111 cases of esophageal cancer. *Huaren Xiaohua Zazhi*, 1998;6(Suppl 7):408
- Yin YB. Advances in radiotherapy for the treatment of esophageal cancer in China. *Huaren Xiaohua Zazhi*, 1998;6(Suppl 7):15-16
- Wu SG, Li DB, Xin BQ, Chen JL, Wang GD. High-dose short time preoperative radiotherapy of esophageal cancer. *Huaren Xiaohua Zazhi*, 1998;6(Suppl 7):421
- Parker SL, Tong T, Bolden S, Wingo PA. Cancer statistics, 1996 (abstract). *Ca Cancer J Clin*, 1996;65:5-27
- Swisher SG, Holmes EC, Hunt KK, Doty JE, Zinner MJ, McFadden DW. The role of neoadjuvant therapy in surgically resectable esophageal cancer. *Arch Surg*, 1996;131:819-825
- Naunheim KS, Petruska PJ, Roy TS, Schlueter JM, Kim H, Baue AE. Multimodality therapy for adenocarcinoma of the esophagus. *Ann Thorac Surg*, 1995;59:1085-1091
- Forastiere AA, Orringer MB, Perez-Tamayo C, Urba SG, Zahurak M. Preoperative chemoradiation followed by transhiatal esophagectomy for carcinoma of the esophagus: final report. *J Clin Oncol*, 1993;11:1118-1123
- Walsh TN, Noonan N, Hollywood D. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N Engl J Med*, 1996;335:462-467
- Lin CH. A new method of extensive resection for gastric carcinoma: selective type III operation. *World J Gastroenterol*, 1998;4:264-265
- Wu XY, Zhang XF, Yin FS, Cai JC, Guan GX. Surgical treatment of residual stomach cancer with a new technique of alimentary tract reconstruction. *World J Gastroentero*, 1998;4(Suppl 2):69-70
- Lin CH. Resection of gastric carcinoma with preservation of pancreas and clearance of lymph nodes along splenic artery: theory, technique and results. *World J Gastroentero*, 1999;5:81-83
- Akahoshi K, Chijiwa Y, Tanaka M, Harada N, Nawata H. Endosonography probe-guided endoscopic mucosal resection of gastric neoplasms. *Gastrointest Endosc*, 1995;42:248-252
- Torii A, Sakai M, Kajiyama T, Kishimoto H, Kin G, Inoue K, Koizumi T, Ueda S, Okuma M. Endoscopic aspiration mucosectomy as curative endoscopic surgery: analysis of 24 cases of early gastric cancer. *Gastrointest Endosc*, 1995;42:475-479
- Jia KL, Yang XL, Zhang JC, Ma LS, Guo TM. Advances in the study of gastric precancer diseases. *Xin Xiaohuabingxue Zazhi*, 1993;1(Suppl 1):17-19
- Wang GT. Progress in the diagnosis and treatment of early gastric cancer. *Huaren Xiaohua Zazhi*, 1998;6(Suppl 7):62-65
- Noguchi Y, Imada T, Matsumoto A, Coit DG, Brennan MF. Radical surgery for gastric cancer: a review of the Japanese experience. *Cancer*, 1989; 64:2053-2062
- Roder JD, Böttcher K, Siewert JR, Busch R, Hermanek P, Meyer HJ, the German Gastric Carcinoma Study Group. Prognostic factors in gastric carcinoma: results of the German gastric carcinoma study 1992. *Cancer*, 1993;72:2089-2097
- Zhou WQ. Endoscopic diagnosis of 506 cases of early gastric cancer. *Shijie Huaren Xiaohua Zazhi*, 1999;7:668
- Zhuang XQ, Sun GH, Zhang YF. Value of foetal-tumorantigen, X-ray, and endoscopy in the diagnosis of early and middle gastric cancer. *Shijie Huaren Xiaohua Zazhi*, 1999;7:545-546
- Antonoli DA. Precursors of gastric carcinoma: critical review with a brief description of early gastric cancer. *Hum Pathol*, 1994;25:994-1005
- Gundersen LL, Sosin H. Adenocarcinoma of the stomach: areas of failure in a re-operation series (second or symptomatic look): clinicopathologic correlation and implications for adjuvant therapy. *Int J Radiat Oncol Biol Phys*, 1982;8:1-11
- Weng HR, Yang WP, Yang JS, Chen YQ, Chen YP, Yang XH. Analysis of 100 dead cases of cardiac carcinoma metastasis after operation. *Huaren Xiaohua Zazhi*, 1998;6:234-235
- Lu DD. Survival analysis of late-staged gastric cancer patients after adjuvant chemotherapy. *Huaren Xiaohua Zazhi*, 1998;6:803
- Yang QL, Li L, Li JQ, Guo WX. Clinical observation on the effects of reformed FAM programme in the treatment of late-staged gastric cancer. *Huaren Xiaohua Zazhi*, 1998;6(Suppl 7):408
- Lin YJ. Further improvement of therapy results for gastric cancer. *Huaren Xiaohua Zazhi*, 1998;6(Suppl 7):8-9
- Wilker H, Preusser P, Fink U. Preoperative chemotherapy in locally advanced and nonresectable gastric cancer: a phase two study with etoposide, doxorubicin, and Cisplatin. *J Clin Oncol*, 1989;7:1318-1326
- Kelsen D, Karpeh M, Schwartz G, Gerdes H, Lightdale C, Botet J, Lauers G, Klimstra D, Huang Y, Saltz L, Quan V, Brennan M. Neoadjuvant therapy of high-risk gastric cancer: a phase III trial of preoperative FAMTX and postoperative intraperitoneal fluorouracil-cisplatin plus intravenous fluorouracil. *J Clin Oncol*, 1996;14: 1818-1828
- Lowy A, Leach S, Mansfield P. Response to neoadjuvant chemotherapy best predicts survival after curative resection of gastric cancer. Presented at the society of surgical oncology 49th annual cancer symposium; Atlanta, Georgia, 1996
- Zou SC, Qiu HS, Zhang CW, Tao HQ. A clinical and long-term follow-up study of peri-operative sequential triple therapy for gastric cancer. *World J Gastroenterol*, 2000;6:284-286
- Abe M, Takahashi M. Intraoperative radiotherapy: the Japanese experience. *Int J Radiat Oncol Biol Phys*, 1981;7:863-868
- China Ministry Of Health. Gastric cancer. In: China Ministry Of Health, ed. *Diagnosis and treatment criteria for common malignancies in China 2*. Beijing: The Joint Publishing House of Beijing Medical University and China Saint Medical University, 1991:52-53