RESEARCH COMMUNICATION

Comparisons of Curative and Side Effects of Chemoradiotherapy among Xinjiang Han, Uigur and Kazakh Esophageal Carcinoma Patients

Li Zhang*, Li-Li Ma, Jian-Qing Zhang, Mei Yang, Tu-Er Xun, Ai Li

Abstract

Objective: This study aimed to explore the differences in the curative and side effects of chemoradiotherapy on esophageal cancer (EC) among Xinjiang Han, Uigur and Kazakh patients. Methods: 170 patients with IIA stage-IV of esophageal squamous cell carcinoma were analyzed retrospectively. Based on different nationalities, they were divided into the Han, Uigur and Kazakh groups. The 1-, 2- and 3-year survival rates, incidence of the side effects (including hematological toxicities, radioactive esophagitis and percutaneous reactions) and application of antibiotics and harmonics were compared among the groups. There was no significant difference in the short-term curative effects among the Han, Uigur and Kazakh groups. The 1- 2- and 3-year survival rates of the three groups were 84%, 40%, 26%; 78%, 27%, 18%; and 60%, 21%, 12% (x^2=14.497, P<0.05). The incidence rate of hamatological toxicity ≥Grade 2 in the Kazakh group was significantly lower than that in the Han or Uigur group. Results: The incidence rates of radioactive esophagitis and percutaneous reactions Grade 2 in the Han group were significantly higher than those in the Uigur or Kazakh group. There was no significant difference in the types of applied antibiotics among the groups, but there were significant differences in the days of antibiotic application and proportion of patients receiving harmonics between the Hans and either of other groups. Conclusion: Chemoradiotherapy shows a better effect in the long-term survival rate among Han EC patients compared with Uigur or Kazakh EC patients. Uigur and Kazakh patients show a better tolerance to the side effects of chemoradiotherapy compared with Hans.

Keywords: Minority - esophageal cancer - chemoradiotherapy - curative effects

Asian Pacific J Cancer Prev, **13**, 169-173

Introduction

Esophageal carcinoma (EC) is one of the most common malignant cancers. It ranks the eighth among the incidence rates of various tumors. Particularly in China, its incidence is 20 times high of that in western Africa (Parkin et al., 2005). Xinjiang is one of the highest EC incidence areas in China. There, minority patients occupy a great proportion of all EC patients, among which the highest incidence is found in Kazakh population and the second in Uigurs (Zhou et al., 2009). Minority EC patients are different from Han patients in living habits and constitution, and the pathogenesis of EC among minorities is also somewhat different from that among Hans (Liu et al., 2011). In China, esophageal squamous cell carcinoma is the major pathological form of EC and esophageal adenocarcinoma only accounts for 0.4% of EC cases (Zou et al., 2002). In recent years, treatment of esophageal squamous cell carcinoma has got great development, but its mortality still stays stubbornly high. In China, EC occupies the fourth place among various malignant cancers causing death (Mariette et al., 2007). Due to lack of an effective method for early diagnosis, 80% of EC cases has developed into moderate or advanced EC at the time of final diagnosis, whose five-year survival rate and median survival are only 15-20% and 18 months, respectively (Jemal et al., 2004). To date, radiotherapy is the most important non-operative protocol in EC treatment, and concurrent chemoradiotherapy is accepted generally as the standard model for non-operative EC treatment (Neuner et al., 2009). But chemoradiotherapy still fails in achieving a satisfactory curative effect up to now. Among various treatment failures, most are caused by local recurrence and failure, which can account for 60-80%. Concurrent chemoradiotherapy and hyperfractionation can increase the survival and local control rates. But on the other hand, they can also aggravate radioactive esophageal injuries (Dillman et al., 1996; Fu et al., 2000; Park et al., 2003), which, in turn, affect the progression of chemotherapy and its curative effect. Actually, there have been reports on individualized adjustment of chemotherapeutic dose in EC treatment according to myelotoxicity (Jordan et al., 2003), but the main reason for dose limitation is under the consideration of late complications after chemotherapy

*Cancer Center of The First Affiliated Hospital of Xinjiang Medical University, Xinjiang, Urumqi, China *For correspondence: lizhangcn@126.com*

(Withers, 1992). Generally, it is at least two months later after chemotherapy that late complications show their symptoms, among which some may even take several years (Slvain et al., 1993).

Till now, a lot of studies on the pathogenesis and epidemiology of EC among Xinjiang different nationalities have been reported, but rare of them has focused on the possible differences in curative and side effects of chemoradiotherapy among different nationalities.

Therefore, this study makes a retrospective analysis of the differences in the curative and side effects of chemoradiotherapy among Xinjiang Han, Uigur and Kazakh EC patients, which is expected to provide a clinical basis for individualized treatment for different ethnic EC patients.

Materials and Methods

Data

A total of 170 patients with IIA-IV esophageal squamous cell carcinoma were analyzed retrospectively. They received treatment in The First Affiliated Hospital of Xinjiang Medical University between May 2008 and May 2010. Among them, 62 patients were Hans, 60 were Uigurs and 48 were Kazakhs. All of their life spans were anticipated more than three months.

Conventional radiotherapy

The approach of analog machine localization was adopted. The lumen presented by esophageal barium swallow was taken as the center for radiation. Non-isocentral anterior vertical Field 1 and isocentral posterior oblique Field 2 were designed. The width of the anterior field was 6 cm and that of the posterior was 5 cm, with the enlargement above and beneath the focus by 3 cm and 4 cm, respectively. 6MV-X rays were applied with the dose prescribed to the primary focus at 60-66 Gy/30-33 f and the preventive dose at 50 Gy/25 f.

Three-dimensional conformal radiotherapy

CT simulative body localization was performed, and thoracic CT scanning was then carried out. The CT images were conveyed by LAN. Tumor target areas were delineated according to the esophagograms, target areas delineated under the esophagoscope, CT-PET and endo-luminal ultrasound. After confirmation of the target areas, radiation fields were designed. After proofreading of the radiation fields from the accelerator, the radiotherapeutic plan was implemented. The radiation range included the recurrent areas and their corresponding nodal drainage areas. The radiation dose was prescribed at 60-66 Gy/30-33 f.

Chemotherapy

A two-drug scheme was performed on the basis of platinum drugs, FP (fluorouracil at 500 mg/m2 on d 1-5 plus cisplatin at 70 mg/m2 on d 1), TP (docetaxel at 75 mg/m2 on d 1 plus cisplatin at 70 mg/m2 on d 1, or paclitaxel at 135-150 mg/m2 on d 1 plus cisplatin at 70 mg/m2 or carboplatin at 300 mg/m2 on d 1) or NP (Vinorelbine at 25 mg/m2 on d 1 and d 8 plus cisplatin at 70 mg/m2 on d 1). 4-6 cycles were prescribed with 28 days as a cycle.

Concurrent chemoradiotherapy

Radiotherapy was performed on d 1 of chemotherapy. Two cycles of chemotherapy were implemented during radiotherapy, leaving 2-4 more cycles after radiotherapy.

Evaluation criteria

Short-term curative effects were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) by WHOM. After chemotherapy, results obtained by X-rays of barium swallow and CT were divided into complete remission (CR), partial remission (PR), no change (NC) and progressive deterioration (PD). Side effects were evaluated according to the effects of chemotherapy on bone marrow suppression according to the classification of toxic reactions to anti-tumor drugs by WHO. Radiation injuries were evaluated according to RTOG criteria (Cox et al., 1995).

Statistical analysis

Data were analyzed by SPSS16.0 software package and x2 test was carried out. Survival rates were determined by Kaplan-Meier and differences were tested by Logrank. $P < 0.05$ was considered statistically significant.

Results

Clinical data

The clinical data are shown in Table 1. x2 test showed that there were no significant differences among the three groups ($P > 0.05$).

Short-term curative effects

In the Han group, 19 cases of CR, 18 of PR, 17 of NC and 8 of PD were found. In the Uigur group, 14 cases of CR, 20 of PR, 15 of NC and 11 of PD were found. And in the Kazakh group, 13 cases of CR, 14 of PR, 12 of NC and 9 of PD were found ($x^2=1.677$, $P>0.05$).

Survival rates

The 1-, 2- and 3-year survival rates of the Han group were 84%, 40% and 26%, those of the Uigur group were 78%, 27% and 18%, and those of the Kazakh group were 60%, 21% and 12%, respectively. The survival rates of the Han group were higher than those of the Uigur group

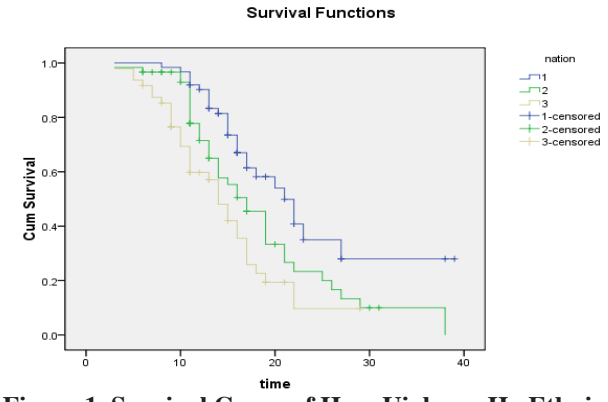

Figure 1. Survival Curve of Han, Uighurs, Ha Ethnic During 1, 2, 3-year. 1: Han; 2: Uighurs; 3: Ha

Table 1. Clinical Data Characteristics of 170 Cases of Han, Uygur, Kazakh Ethnic Patients with Esophageal Cancer

	Han ethnic	Wei ethnic	Ha ethnic	Chi-square value	P value
Gender					
Male	44	47	40	2.425	0.297
Female	18	13	8		
Age					
	60.5±9.68	57.6±10.4	57.4±8.56	7.122	0.056
	60.1±25.6	63.9±24.6	63.0±2.06	0.922	0.398
Stage					
Phase IIA	15	11	9	2.663	0.85
Phase IIB	5	9	6		
Phase III	28	23	20		
Phase IV	14	17	13		
Cervical and upper thoracic	12	9	13	2.922	0.571
Lesion sites					
Chest section	42	39	30		
Thoracic	8	12	5		
Narrow type	19	18	18	3.824	0.7
Ulceration	11	16	7		
X-ray type					
Medullary	22	19	18		
Protruded	10	7	5		
Lesion length					
<10cm	32	36	31	1.99	0.37
≥10cm	30	24	17		
Concurrent chemotherapy and radiotherapy					
Yes	26	29	16	20468	0.291
No	36	31	32		
Treatment					
Radical radiotherapy	46	49	38	1.034	0.596
Postoperative radiotherapy	16	11	10		
Radiotherapy approach					
Appropriate line	28	31	23	0.52	0.771
Conventional	34	29	35		

Table 2. Comparison of Toxicity in Han, Uygur, Kazakh Ethnic Patients with Esophageal Cancer (cases, %)

Index	Han ethnic	Wei ethnic	Ha ethnic	Chi-square value	P1/P2/P3
Leukopenia					
0	22	25	24	3.204	0.757/0.232/0.434
1	34	29	22		
2	6	6	2		
Hemoglobin reducing					
0	10	13	13	15.149	0.046/0.011/0.780
1	22	31	26		
2	14	11	6		
3	16	15	3		
Thrombocytopenia					
0	10	14	15	14.116	0.025/0.035/0.785
1	24	33	23		
2	23	8	7		
3	5	5	3		
Radiation esophagitis					
1	30	39	35	7.425	0.064/0.009/0.379
2	32	21	13		
Skin reactions					
1	33	48	38	13.085	0.002/0.005/0/915
2	29	12	10		
Type of antibiotic					
Generation I cephalosporin	25	30	24	1.83	0.561/0.523/0.868
Generation II cephalosporin	27	22	16		
Generation I II cephalosporin	10	8	8		
Days of antibiotic usage					
<5 days	18	39	31	22.546	0.000/0.001/0.999
5-7 days	39	16	13		
>7 days	5	5	4		
Hormone usage					
yes	38	21	14	13.781	0.040/0.050/0.520
no	24	39	34		

P1, Comparison of Han and Uygur ethnic; P2, Comparison of Han and Ha ethnic; P3, Comparison of Wei and Ha ethnic

or the Kazakh group, showing significant differences (x2=14.497, P<0.05). But no significant difference was found between the Uigur and Kazakh groups (P>0.05).

Side effects

Hematological toxicities

Hematological toxicities ≥Grade 2 occurred in all groups. The incidence rates of a decrease in hemoglobin of the Han, Uigur and Kazakh groups were 46.1%, 43.3% and 18.8%, respectively (x^2=15.149, P<0.05). The incidence rates of thrombocytopenia of the three groups were 45.2%, 21.7% and 20.8%, respectively (x^2=14.116, P<0.05). The results indicated that the incidence rates of hematological toxicities in the Kazakh group are significantly lower than those in the Han or Uigur group.

Radioactive esophagitis

The incidence rates of radioactive esophagitis ≥ Grade 2 of the Han, Uigur and Kazakh groups were 51.6%, 35.0% and 27.1% (x^2=7.425, P<0.05). A significant difference was found between the Han and the minority groups (P<0.05), but no significant difference was found between the Uigur and Kazakh groups (P>0.05).

Percutaneous reactions

The incidence rates of percutaneous reactions ≥ Grade 2 of the Han, Uigur and Kazakh groups were 46.7%, 20.0% and 20.8% (x^2=13.085, P<0.05). The incidence rate of the Han group was significantly higher than that in the Uigur or Kazakh group (P>0.05), but there was no significant difference between the Uigur and Kazakh group (P>0.05).

Application of antibiotics and harmonics

The types of antibiotics, administration days and application of harmonics or not in the three groups during treatment of esophagitis were analyzed. There were no significant differences in the types of antibiotics used during treatment among the three groups (x^2=1.830, P>0.05). Taking 5-7 d of antibiotic use as an important indicator (as patients receiving 5-7 d of antibiotics took a great proportion in each group, which would be convenient for the sake of comparisons among groups), the proportions of the three groups were 62.9 %, 26.7 % and 27.0 %, respectively (x^2=22.546, P<0.05), showing a significant difference between the Han group and either of

the other two groups. The proportions of patients receiving harmonics during anti-inflammatory treatment in the three groups were 61.3%, 35.0% and 29.1%, respectively (x^2=13.781, P<0.05), showing a significant difference between the Han group and either of the other two groups (P<0.05) (Table 2).

Discussion

Chemoradiotherapy is the standard model in treatment of locally advanced EC nowadays. A clinical study on Stage III EC provided in PTOG8501 reported that concurrent chemoradiotherapy could achieve a better curative effect in treatment for those inoperative patients with moderate or advanced EC compared with radiotherapy alone (Cooper et al., 1999). Wong et al proved further that concurrent chemoradiotherapy possessed advantages in long-term survival and local control rates after conducting a Meta analysis of multiple random comparative studies (Wong and Malthaner, 2006). The incidence of EC displays apparent regional differences as well as a certain degree of ethnic differences (Doornum et al., 2003; Si et al., 2003), which suggests that population has genetic susceptibility to EC, and genetic backgrounds and environmental factors both play particular roles in the genesis and development of EC. Therefore, it is very likely that EC patients also show some differences in treatment responses and tolerance as results of ethnic differences.

The Kazakh population in Xinjiang is a nationality with a high EC incidence (Zeng et al., 2011). But the differences in treatment effects and tolerance of this nationality from others have seldom been reported. In this study, the curative and side effects of chemoradiotherapy on EC among three major nationalities in Xinjiang (Han, Uigur and Kazakh, respectively) were compared and analyzed. The results showed that there were no significant differences in the short-term curative effects among the three groups, but there were significant differences in the long-term curative effects (even though the results of the long-term curative effects of the Han patients were a little different from those in another report, in which the reported 1- and 3-year survival rates after three-dimensional conformal radiotherapy were 73.6% and 50.9% (Ma et al., 2010). The lower long-term survival rates among the Uigur and Kazakh patients compared to the Hans may be caused by the following reasons, a larger proportion of the Han patients who received radical operation and concurrent chemoradiotherapy, a poorer treatment compliance from the minority patients due to such factors as ethnic customs, religious beliefs, economic conditions, etc., and the potential molecular markers for prediction of the curative effects which may be different from nationality to nationality. A study on related genes and proteins of early EC in Xinjiang Kazakh patients has been reported, in which ten highly-related early tumor-causing genes (such as survivn, edc42, bmp, etc.) were found out, and by analyzing their correlations preliminarily with pathological grading as well as the roles played by their corresponding genomes in methylation, the genes and genomes that were closely correlated with the genesis and development of early EC among the Kazakh population were identified (Zhou et al., 2009). However, due to the limitation that only a small sample is involved in this current study, it will be necessary to carry out follow-up toward a larger-scale sample for further verification.

Application of chemoradiotherapy is influenced by ethnic differences, and Chinese population displays a poorer tolerance to chemoradiotherapy compared with western populations (Kleinberg et al., 2003). The present study showed that Uigur and Kazakh EC patients display a much better tolerance to possible adverse reactions during chemoradiotherapy than Han patients. Presumably, such a difference may be caused by the following reasons: (Parkin et al., 2005) 1) Food habits:The minority patients have special food habits, such as hot tea with milk, smoked meats and homemade milk products as staple foods, less fresh vegetables or fruits, etc. Though their food habits are correlated closely with the high incidence of EC, they also give rise to a better tolerance to treatment and lower incidence rates of serious adverse reactions on the other side. In addition, most of the minority patients are farmers and herdsmen who mainly take up physical labor (Zhou et al., 2009). 2) Age of the onset of EC: The data in this present study showed that the proportion of the minority EC patients whose onset age was less than 60 years old is larger compared to the Han patients, which may bring about differences in PS and less complications of other medical diseases (Liu et al., 2009). 3) Differences in life quality:Though radioactive esophagitis seldom imperils patients' life after treatment, it often reduces the patients' life quality during chemotherapy, or even influences the long-term curative effect of the patients negatively. The pains caused by radioactive esophagitis force some patients to suspend radiotherapy temporarily, and some may even refuse to receive further treatment after suffering from the pains. Li Zhang et al once conducted an investigation into life qualities of Xinjiang Han, Uigur and Kazakh EC patients who underwent radiotherapy, and the results showed that the best life quality is found among the Uigur patients, better among the Han patients and the worst among the Kazakh (Zhang et al., 2011). The underlying reasons may be that different awareness and expectation values of the disease can be formed as results of different religious beliefs.

Xinjiang is an area in which multiple nationalities live together. Thus, individualized treatment schemes should be designed according to different curative effects and tolerance of different nationalities in EC treatment.

This study has some limitations. As only a small sample was involved in this study, a larger sample is necessitated in order to verify the above-obtained results in the future. In addition, the reasons underlying the different curative effects and tolerance among different nationalities still need further exploration.

References

Cooper JS, Uo MD, Herskovic A, et al (1999). Chemo-radiotherapy of locally advanced esophageal cancer: long term follow –up of a prospective randomized trial (RTOG 8501). Radiat Therapy oncol Group. *JAMA*, **281**, 1623-7.

Cox JD, Stetz J, Pajak TF (1995). Toxicity criteria of the

radiation therapy oncology group (RTOG) and the European organization for research and treatment of cancer (EORTC). *Int J Radiat Oncol Biol Phys*, **31**, 1341-6.

Dillman RO, Herndon J, Seagren SL, et al (1996). Improved survival in stage III non-small cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. *J Natl Cancer Inst*, **88**, 1210-5.

Doornum V, Korse CM, Buning-Kager JC, et al (2003). Reactivity to human papillomavirus type 16 L1virus-like particles in sera from patients with genital cancer and patients with carcinomas at five different extra-genital sites. *Br J Cancer,* **88**, 1095-100.

Fu KK, Pajak TF, Trotti A, et al (2000). A radiation therapy oncology group (RTPOG) phase III randomized study to compare hyper-fractionation and two variants of accelerated fractionation to standard fractionation radio-therapy for head-and neck squamous cell carcinomas:first report of RTOG 9003. *Int J Radiat Oncol Biol Phys*, **48**, 7-16.

Jemal A, Clegg LX, Ward E, et al (2004). Annual report to the nation on the status of cancer, 1975–2001, with a special feature regarding survival. *Cancer*, **101**, 3-27.

Jordan SD, Poole CJ, Archer VR, et al (2003). A retrospective evaluation of the feasibility of intrapatient dose escalation as appropriate methodology for dose-ranging studies for combination cytotoxic regimens. *Cancer Chemother Pharmacol*, **52**, 113-8.

Kleinberg L, Knisely JP, Hritmiller R, et al (2003). Mater survival results with preoperative cisplatin, protracted infusion 5-fluorouracil,and44-GY radiotherapy for esophageal cancer. *Int J Radiat Oncol Biol*, **56**, 358-34.

Liu Z, Feng JG, Tuersun A, et al (2011). Proteomic identification of differentially-expressed proteins in esophageal cancer in three ethnic groups in Xinjiang. *Mol Biol Rep*, **38**, 3261-9.

Ma HB, Zhang XZ, Wang XJ, et al (2010). Effects of three-dimensional conformal radiotherapy on the esophageal carcinoma. *Chinese-German J Clin Oncol*, **9**, 579-82.

Mariette C, Piessen G, Triboulet JP (2007). Therapeutic strategies in esophageal carcinoma: role of surgery and other modalities. *Lanett Oncol*, **8**, 545-53.

Neuner G, Patel A, Suntharalingam M (2009). Chemo-radiotherapy for Esophageal Cancer. *Gastrointest Cancer Res*, **3**, 57-65.

Park J, Ahn YC, Kim H, et al (2003). A phase IItrial of concurrent chemo-radiation therapy followed by consolidation chemotherapy with oral etopo-side and cisplatin for locally advanced inoperable non-small cell lung cancers. *Lung Cancer*, **42**, 227-35.

Parkin D, Bray F, Ferlay J, et al (2005). Global Cancer Statistics, 2002. *CA Cancer J Clin*, **55**, 74-108.

Si HX, Tsao SW, Poon CS, et al (2003). Viral load of HPV in esophageal squamous cell carcinoma. *Int J Cancer*, **103**, 496-500.

Slvain C, Barrioz T, Besson I, et al (1993). Treatment and long-term outcome of chronic radiation esophagitis after radiation therapy for head and neck tumors. *Diq Dis Sci*, **38**, 927-31.

Withers HR (1992). Biologic basis of radiation therapy. In: Perez CA, Brady LW, editors. Principles and practice of radiation herapy (2nd ed), JB Lippincot. Philadelphia, pp, 64-98,

Wong RK, Malthaner R (2006). Combined chemotherapy and radiotherapy (without surgery) compared with radiotherapy alone in localized carcinoma of the esophagus. *Cochrane Database Syst Rev*, **1**, CD002092.

Zeng T, MaY, Xu L, et al (2011). A 1: 2 Case-control Study of Tap2/HLA-DR9 Gene Polymorphism with Esophageal Cancer in Kazakh. *Cancer Res Prev Treat,* **38**, 210-3.

Zhang L, Li Q, Zhang JQ, et al (2011). Investigation and analysis on quality of life and related impact parameters of Han and minority nationality patients with advanced esophageal carcinoma undergoing radiotherapy in Xinjiang. *J Chin Radiat Oncol*, **4**, 295-6.

Zhou SM, SheyhidinI, Yang T, et al (2009). Relationship between human papillomavirus 16 and esophageal squamous cell carcinoma in Uygur population in Xinjiang Uygur Autonomous Region. *World Chin J Digestol*, **17**, 3214-7.

Zou X, Lu F, Zhang X, et al (2002).Characteristics of esophageal cancer mortality, in China, 1990/1992. *Bull Chin Cancer*, **11**, P446-9.