Clin Oncol Cancer Res (2009) 6: 290-295
DOI 10.1007/s11805-009-0290-9

Analysis of Prognostic Factors of Esophageal and Gastric Cardiac Carcinoma Patients after Radical Surgery Using Cox Proportional Hazard Model-A Random Sampling Study from the Fourth Hospital of Hebei Medical University during the Period of 1996-2004

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This work was supported by the Hebei Provincial Program for the Subjects with High Scholarship and Creative Research Potential, China.

Received April 18, 2009; accepted June 21, 2009.

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OBJECTIVE To retrospectively analyze clinical data of patients from our hospital who underwent radical surgery for esophageal carcinoma and for adenocarcinoma of the gastric cardia, as well as to investigate prognostic factors affecting the long-term survival of the patients.
METHODS Data from the patients eligible for our study, admitted to the 4th Hospital of Hebei Medical University from January 1996 to December 2004, were randomized, and 12 distinctive clinicopathologic factors influencing the survival rate of those who underwent radical surgery for esophageal carcinoma or carcinoma of the gastric cardia were collected. Univariate and multivariate analysis of these individual variables were performed using the Cox proportional hazard model.
RESULTS It was shown by univariate analysis that age, tumor size, pathologic type, lymph node status, TNM staging, depth of infiltration and encroachment into local organs, etc., were the factors that markedly influenced the prognosis of patients ($P < 0.01$). Multivariate analysis showed that pathologic type, number of the lymph node metastases, involvement of local organs, and TNM staging were independent prognostic factors ($P < 0.05$).
CONCLUSION The independent factors influencing the prognosis of patients with esophageal cancer and carcinoma of the gastric cardia include pathologic type, number of lymph node metastases, involvement of local organs and TNM staging. The main prognostic factors affecting the patient's survival are patient age, tumor size and depth of infiltration. In addition, patients with involvement of the local organs have a worse prognosis, and they should be closely followed up.

KEY WORDS: esophageal carcinoma, carcinoma of gastric cardia, Cox model, prognosis.

Introduction

Until now the prognostic indicators of the patients with esophageal carcinoma and carcinoma of the gastric cardia has not been defined specifically. In our study, clinical data from esophageal and gastric cardiac cancer cases from the 4th Hospital of Hebei Medical University, during a period from January 1996 to December 2004 (9 years total), were retrospectively analyzed, and the factors affecting the prognosis of patients who underwent radical surgery for esophagocardiac cancer were investigated.

Materials and Methods

Clinical data

During the period of 9 years, 6,104 patients with esophageal cancer and carcinoma of the gastric cardia were admitted to the 4th Hospital of Hebei Medical University. They received initial treatment including surgery without undergoing preoperative radiotherapy or chemotherapy. All of these patients had lived in the Hebei province for over 10 years, and had received a conclusive histopathologic diagnosis. A random sampling was made in 1,526 of the total patients, and follow-up was conducted in 1,414 of the 1,526 patients who had undergone radical surgery. The deadline for the follow-up was December 31, 2006. Follow-up of the sample cases was conducted by phone and sometimes in combination with mail. The follow-up started at the time of surgery and ended at the patient's death. Failure to come to follow-up visits or the date of the last visit was defined as the ending point of the follow-up, and death due to the tumor was defined as the end result.

Statistical analysis

Chi-square test was used for enumeration of the data, Kaplan-Meier curve for calculation of the survival rate, and COX proportional hazard model for univariate and multivariate analysis. SPSS13.0 was used for all the statistical calculations involved in our study, with $\alpha = 0.05$ as the significance level of statistically significant differences.

Results

In our study, follow-up of 1,414 patients undergoing radical surgery was conducted, with 906 returning feedback forms. The representation by 906 patients is satisfactory, and can represent the prognosis of the 1,414 patients with radical surgery.

General data

Gender

A total of 65 patients were male (73.4%) and 241 female (26.6%), with a male-female ratio of 2.76 *vs.* 1, which is generally consistent with the characteristic male-female ratio composition in this high risk region.

Age

Using the age of the patient at the time of operation, the age of the patients in our group ranged from 24 to 80 years old, with an average of 57.82 ± 8.6, and a median age of 58. Based on the age distribution of the patients, the cases were divided into 3 age groups, i.e. the group with ≤ 50 years (201 cases), with a range of 51-60 years (345 cases), and with > 60 years (359 cases).

Sites

Disease at the superior thoracic segment occurred in 68 cases (7.5%), lesions of the middle thoracic segment were found in 421 (46.5%), those of the inferior thoracic segment occurered in 86 (9.5%), and those of the gastric cardia in 331 (36.5%).

Size of tumor

There was loss of the initial data in 3 of the 906 cases. In the other 903 cases, there were 181 cases with a maximum tumor size of ≤ 3 cm (20%), 387 cases with a size of 3.1-5.0 cm (42.7%), 201 cases with 5.1-7 cm (22.2%), and 134 with > 7.0 cm (14.8%).

TNM staging

There was a failure of TNM staging in 2 cases owing to uncertain postoperative pathologic results. In the other cases, there were 95 patients with Stage-0 and I tumors (10.5%), 377 with Stage-II (41.6%), 316 with Stage-III (35.0%), and 116 with Stage-IV (12.8%).

COX survival analysis

There was no significant difference in the death risk among the groups, based on factors, such as gender, site of tumor, type of surgical incision, postoperative residual tumor, and vascular tumor embolus ($P > 0.05$). Thus there was no correlation between the above mentioned factors and the prognosis of the patients. However, based on the age distribution, the prognosis seemed better in the patients from the age group of 51-60 years, compared to the age group of ≤ 50 and > 60 years. Regarding the size of the tumor, with an increase of the tumor size, there was an increase in the death risk, compared to the group with tumors ≤ 3 cm. As for pathologic type, with the exclusion of undifferentiated small-cell carcinoma (USCC), there was no significant difference in the death risk among the other pathologic types compared to the commonly seen squamous carcinoma (SqCa). In the cases with positive lymph nodes, as the number of the lymph node metastases increased, there was a tendency of the death risk to increase as well, compared to the cases with negative lymph nodes. As far as TNM staging was concerned, compared to the Stage 0 and I cases, the more advanced the TNM staging, the higher the death risk. In regards to the depth of infiltration, compared to cases with carcinoma in situ, the death risk would obviously be increased once there was an encroachment of tumor into local tissue. Moreover, the death risk of the cases with encroachment into local organs was significantly higher compared to those without encroachment. The result of univariate analysis showed that factors, such as age, tumor size, pathologic type, lymph node status, clinical stage, depth of infiltration, and infiltration of local organs, were the significant factors influencing the prognosis of the patients ($P < 0.05$). For univariate analysis, see Table 1.

Table 1. Univariate analysis of prognostic factors of 906 patients with esophageal carcinoma and carcinoma of gastric cardia after surgery.

Factors	Wald	*P*	RR	95.0% CI for RR
Age (years)	10.061	0.007		
≤ 50	2.506		0.1	.
51-60	9.759	0.002	0.798	0.663 ± 0.963
> 60		0.113	1.337	0.934 ± 1.916
Tumor size (cm)	40.165	0.000		
≤ 3			1.000	
3.1-5	13.743	0.000	2.676	1.590 ± 4.502
5.1-7	11.134	0.001	2.586	1.480 ± 4.518
> 7	36.299	0.000	5.416	3.126 ± 9.383
Pathologic type	25.928	0.000		
SqCa			1.000	
Adenocarcinoma	.809	0.369	1.151	0.847 ± 1.563
USCC	24.006	0.000	3.874	2.254 ± 6.660
Mucinous adenocarcinoma	1.951	0.163	1.895	0.773 ± 4.648
Others	1.620	0.203	1.706	0.749 ± 3.884
No. of lymph node metastasis	45.295	0.000		
0			1.000	
1-3	22.699	0.000	2.094	1.545 ± 2.838
> 3	36.954	0.000	3.608	2.385 ± 5.456
TNM staging	28.258	0.000		
Stage-0 & I			1.000	
Stage-II	6.487	0.011	2.591	1.245 ± 5.393
Stage-III	15.935	0.000	4.380	2.121 ± 9.045
Stage-IV	17.583	0.000	5.162	2.397 ± 11.118
Depth of infiltration	21.650	0.001		
Tumor in situ			1.000	
Lamina propria, Submucosa	1.202	0.273	.368	0.061 ± 2.200
Superficial muscular layer	0.885	0.347	1.835	0.518 ± 6.504
Deep muscular layer	0.303	0.582	1.411	0.414 ± 4.817
Fibrous membrane (Serous membrane)	3.022	0.082	2.776	0.878 ± 8.774
Surrounding soft tissue	3.866	0.049	3.182	1.004 ± 10.087
Encroachment of localorgans	27.798	0.000		
Negative			1.000	
Positive			2.382	1.725 ± 3.290

Multivariate analysis

Based on the pathologic types, the death risk of the USCC was 3.359 times as high as that of the SqCa, and the risk of death in the cases with 1 to 3 positive lymph nodes and over 3 were 1.552 and 2.774 times as high as that in the cases without lymphatic metastases, respectively. The death risk in the cases with infiltration into the local organs was 2.050 times as high as that without encroachment of local organs. The death risk in the Stage II, III and IV cases was 2.204, 2.865 and 2.470 times as high as that in the Stag-0 and I cases, respectively. There was a significant difference in the above mentioned statistical analysis ($P < 0.05$). It was shown by multivariate analysis that the pathologic type, number of lymph node metastases, infiltration of local organs, and TNM staging were independent prognostic factors (Table 2).

Table 2. Multivariate analysis of prognostic factors of 906 patients with esophageal carcinoma and carcinoma of gastric cardia after surgery.

Factor	β	SE	Wald	P	RR	95.0% CI for RR	
						Lower	Upper
Pathologic type			22.338	0.000			
SqCa					1.000		
Adenocarcinoma	-0.115	0.203	0.319	0.572	0.891	0.598	1.328
USCC	1.212	0.285	18.042	0.000	3.359	1.920	5.876
Mucinous adenocarcinoma	0.296	0.473	0.393	0.531	1.345	0.532	3.401
Others	0.391	0.426	0.842	0.359	1.479	0.641	3.410
TNM staging			8.005	0.046			
Stage-0 & I					1.000		
Stage-II	0.790	0.379	4.349	0.037	2.204	1.049	4.633
Stage-III	1.053	0.388	7.353	0.007	2.865	1.339	6.131
Stage-IV	0.904	0.454	3.968	0.046	2.470	1.015	6.011
No. of lymph node metastasis			16.314	0.000			
0					1.000		
1-3	0.439	0.195	5.067	0.024	1.552	1.058	2.275
> 3	1.020	0.253	16.312	0.000	2.774	1.691	4.552
Encroachment of localorgans			17.882	0.000			
Negative					1.000		
Positive	0.718	0.170	17.882	0.000	2.050	1.470	2.858

Discussion

In our study, after summarizing the present state of related studies in China and abroad and combined with clinical practice, 12 clinicopathologic factors were selected to conduct a comprehensive analysis, using the UICC-recommended COX proportional hazard ratio model[1,2]. Univariate analysis suggested that the prognosis of patients undergoing radical surgery for esophageal carcinoma and carcinoma of the gastric cardia has no correlation with factors such as gender, tumor site, type of surgical incision, postoperative residual tumor, and vascular tumor embolus, while the age, maximum diameter of the tumor, pathologic type, TNM staging, number of the lymph node metastases, depth of infiltration, and involvement of local organs significantly correlate with the prognosis of the patients receiving radical surgery. Upon adding the related factors into the COX hazard ratio model for the analysis, 4 independent factors related to prognosis of patients undergoing radical surgery for esophageal carcinoma and carcinoma of the gastric cardia were demonstrated. These factors, in order as follows, were: pathologic type, number of the lymph node metastases, TNM staging and involvement of local organs.

Presently, in regards to the correlation between pathologic type and prognosis of esophageal and gastric-cardiac carcinoma patients, the level of tumor differentiation was usually the first topic for discussion, and in general there was a negative correlation between level of the tumor differentiation and prognosis[3]. The correlation between the pathologic type of these cancers and the prognosis of patients with esophageal and gastric cardiac carcinomas was analyzed in our study, since there was relatively less research on these types of cancers. After grouping the related cases in accordance with the postoperative pathologic results, it was found that besides the USCC group, there was no statistical significance in the other pathologic types with respect to the death risk in the SqCa group. Further, the death risk was 3.359 times as high in the USCC group as that in the SqCa group, thus there was a significant statistical difference between the two. These results suggested that the prognosis of the USCC patients was poor, and that clinicians ought to pay more attention to these cases. Immediate postoperative follow-up and other effective measures including adjuvant therapy were used to improve the prognosis.

Concurrently, it is well accepted by many authors from China and overseas that lymphatic metastasis and

the number of positive lymph nodes are the important factors affecting patients with esophageal carcinoma and carcinoma of the gastric cardia; however, the TNM staging method does not involve the number of lymph nodes. The main reason lies in the fact that the relationship between the number of the lymph node metastases and the prognosis of patients is not defined and that related reports are not in agreement on this issue either. For example, it was found by Kimura et al.[4] that there was an apparent correlation between number of the lymph node metastases and prognosis, and that the median survival time of the patients with 3 or more lymph node metastases was 772 d, while that of the patients with 1 to 3 lymph node metastases was 2330 d. When the number of lymph node metastases was over 3, the 5-year survival rate of patients was overtly lower compared to the patients with 3 or fewer lymph node metastases. There was a significant difference between the two. Similar to the study mentioned above, Kawahara et al.[5] believed that patients would have a poorer prognosis if the number of lymph node metastases was beyond 3. However, Wang et al.[6] found that that the patient would have a poor prognosis only if the number of lymph node metastases was beyond 4. It was discovered by the statistical research conducted by our group that the death risk in the patients with 1 to 3 and over 3 lymph node metastases were 1.552 and 2.774 times as high as in those without lymphatic metastases, respectively. Statistical analysis showed there was a significant difference between the death risks, which is basically in conformity with the above mentioned results. Data from larger studies are still needed for the number of lymph node metastases to be introduced into TNM staging system. Nevertheless, what can be affirmed is that the patients with lymphatic metastases should be classified as the high-risk group, with close postoperative follow-up and pertinent adjuvant therapy in order to prevent recurrent metastases.

Although the TNM staging standard on esophageal carcinoma and carcinoma of the gastric cardia remains controversial in academic circles, the current TNM staging and its relation to the prognosis of esophageal and gastric cardiac carcinoma in patients is still well-defined. It has been proven by many authors that the more advanced the TNM stage, the poorer the prognosis for patients[7,8]. In this study, the Cox proportional risk ratio model was used to analyze the correlation between TNM staging and prognosis of the patients who underwent radical surgery for cancer. The death risks in the groups with Stage II, III and IV cancers were, respectively, 2.204, 2.865 and 2.470 times as high as in the groups with Stage 0 and I cancers, showing a significant difference. However compared to the Stage 0 and I cancer groups, the death risk in the Stage III group seemed higher than that in the Stage IV group. No significant difference between the two could be confirmed, since further multiple comparisons studies have not been conducted. The above mentioned results have confirmed that the currently used TNM staging system is precise for suggesting the prognosis of patients. Therefore, in order to raise the postoperative survival rate and improve the prognosis of esophageal carcinoma patients, early diagnosis and early surgical treatment is essential.

In our study, moreover, the death risk in cases with involvement of the local organs, such as the thoracic duct, the azygos vein, part of the thoracic pleural membranes, the lungs, the spleen and the pancreas, was obviously higher than that in the cases without encroachment into the local organs. The reason lies in the fact that lymph vessels are present in the mucosal layer of the esophagus and cardia[9], and after penetration of the muscular layer, the lymph vessels enter the nodes of the local tissues or directly enter the thoracic duct[10]. The anatomic structure of the lymph node thus allows early invasion of tumor into the local organs, and distant metastases might even occur. Generally, the deeper the tumor infiltration is, the higher the probability of the lymphatic metastasis. Therefore, when penetration of the tumor through the seromembranous layer is present and encroachment of the local organs has occurred, the probability of distant metastasis is obviously increased, and the prognosis is relatively poor. In addition, since resection of tumors with surrounding structures is performed in the patients with involvement of other tissue or organs, such as the thoracic duct, the azygous vein, part of the pleura, the lungs, the spleen and the pancreas, a larger incision is required for surgery, which results in hematogenous metastasis of the cancer cells or implantation metastasis. This was also one of the reasons for the poor prognosis of the patients.

Some factors, such as the age, depth of infiltration and tumor size, could not be considered independent prognostic factors because there was usually a close correlation between these factors and the independent prognostic factors. This is especially true with tumor metastases as this factor was very closely related to tumor size and the depth of infiltration[11,12]. An interaction between the correlations might bring about the consequence that the above mentioned factors ultimately failed to enter the multifactorial regression model.

In our study, in combination with data from the related studies in China and abroad, a random sampling was used to analyze the large sample data from the 4th Hospital of the Hebei Medical University. The COX hazard model, which is internationally recommended for survival analysis, can be used to select the factors which could affect the prognosis of patients undergoing radical surgery for esophageal carcinoma and carcinoma of the gastric cardia. It will be of instructive significance for clinicians to intervene, to formulate a therapeutic regimen, to optimize the use of the medical resources, and to supply scientific basis for evaluating the prognosis of patients with esophageal carcinoma and carcinoma of the gastric cardia.

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