Med Oncol (2013) 30:514
DOI 10.1007/s12032-013-0514-y

SHORT COMMUNICATION

Time-varying pattern of recurrence risk for gastric cancer patients

Xing-Yu Feng · Ying-Bo Chen · Wei Wang · Yuan-Xiang Guan · Yuan-Fang Li · Shi Chen · Xiao-Wei Sun · Wei Li · Da-Zhi Xu · You-Qing Zhan · Xiao-Shi Zhang · Zhi-Wei Zhou

Received: 18 January 2013 / Accepted: 16 February 2013 / Published online: 24 February 2013

Abstract This study analyzed the time-varying pattern of the recurrence risk for gastric cancer after surgery. A total of 1,222 gastric patients undergoing D2 resection surgery were studied retrospectively. The annual recurrence hazard curve for all of the populations showed one early peak and a late rise within 10 years after the surgery. The first major recurrence peak covers the first 3 years after the surgery, rising to a maximum at 1.5 years after surgery, followed by a decline until 7.5 years after the surgery, at which point the curve began to rise again. A subgroup analysis of this pattern also revealed that the curves of the patients with bigger tumors, poorly differentiated/undifferentiated adenocarcinomas, lymphatic/venous invasion, T3 and T4, node positive or with fewer lymph nodes retrieved were steeper. Chemotherapy can reduce the hazard rate for recurrence of gastric cancer. Our study confirms the time-varying pattern of the recurrence risk for gastric cancer, and it further supports the hypothesis of tumor dormancy after surgery. To effectively reduce the recurrence risk, new adjuvant therapies beyond chemotherapy may be needed.

Keywords Gastric cancer · Recurrence risk · Tumor dormancy

Xing-Yu Feng and Ying-Bo Chen: contributed equally to this work.

X.-Y. Feng · Y.-B. Chen · W. Wang · Y.-X. Guan · Y.-F. Li · S. Chen · X.-W. Sun · W. Li · D.-Z. Xu · Y.-Q. Zhan · X.-S. Zhang (✉) · Z.-W. Zhou (✉)
State Key Laboratory of Oncology in South China, 651 Dongfeng Road East, Guangzhou 510060, China
e-mail: zhangxsh@sysucc.org.cn

Z.-W. Zhou
e-mail: zhouzhiw@sysucc.org.cn

X.-Y. Feng · Y.-B. Chen · W. Wang · Y.-X. Guan · Y.-F. Li · S. Chen · X.-W. Sun · W. Li · D.-Z. Xu · Y.-Q. Zhan · Z.-W. Zhou
Department of Gastric and Pancreatic Surgery, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou 510060, China

X.-S. Zhang
Biotherapy Center, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou 510060, China

Introduction

Gastric cancer remains one of the most common causes of cancer-related deaths worldwide [1]. The primary cause of gastric cancer-related death is recurrence. However, little research exists concerning the time-varying pattern of the recurrence risk for gastric cancer after surgery. Furthermore, the risks of recurrence were almost universally described using survival curves, which lacked information regarding the changes in the recurrence probability over time [2, 3]. Nevertheless, use of the hazard function statistical method can explain changes in the recurrence rate over time. Other investigators have used this method to find a pattern in the time distribution of the recurrence hazard for breast cancer patients [4, 5], which may indirectly elucidate the biological behavior of breast cancer. In addition to their theoretical value, these findings may spur novel therapeutic approaches and appropriate follow-up strategies [6]. We speculated that there may a similar pattern for gastric cancer.

Patients and methods

This study consisted of 1,222 gastric cancer patients who underwent D2 radical surgery with R0 resection and did

not receive any neoadjuvant chemotherapy or radiotherapy from January 1994 to December 2006 at the Sun Yat-Sen University Cancer Center in Guangzhou, China. This study was conducted in accordance with the Declara tion of Helsinki, and all patients signed a consent form approved by the Research Ethics Committee of the Sun Yat-sen University Cancer Center. The eligibility criteria included a histologically confirmed R0 resection and a postoperative survival time of 3 months, with at least 12 months of follow-up data regarding tumor recurrence and death.

In this study, recurrence-free survival (RFS) was defined as the time from surgery to the earliest occurrence of relapse (local or distant) or to death from the tumor [5]. The survival distributions were estimated using the Kaplan–Meier product-limit method and were compared using the log-rank test. Cox proportional hazards regression was used to model the relationship of RFS with the clinico-pathological parameters. For a graphical display of the RFS, the annual hazard rates were estimated using a Kernel-smoothing method [5, 7]. All of the statistical analyses were performed using the Stata statistical software package 10.0 (Stata Corporation Ltd, College Station, TX, USA).

Results

Nine factors were found to have a statistically significant association with the RFS upon univariate analysis: age, tumor location, tumor size, histological grade, lymphatic/venous invasion, pathological T (pT), pathological N (pN), number of retrieved lymph nodes and chemotherapy (Table 1). All of these variables were included in a multivariate Cox proportional hazards regression analysis, which revealed that all of these variables were independent prognostic factors for RFS (Table 2).

The annual recurrence hazard curve for all of the patients showed a regular curve: one early peak and a late rise within the 10-year period after the surgery. The first major recurrence surge peaks at 1.5 years after the surgery, covering the first 3 years after surgery, which we call the early peak. Then, the hazard curve begins to fall until 7.5 years after the surgery, at which point the curves begin to rise again (Fig. 1). This recurrence pattern was observed in the subgroup analysis according to several clinico-pathological param eters. In patients with a high risk of relapse (e.g., the tumor size >5 cm (Fig. 2a), the poorly differentiated/undifferentiated adenocarcinoma (Fig. 2b), lymphatic/venous invasion positive (Fig. 2c), T3 and T4 (Fig. 2d), node positive (Fig. 2e), retrieved lymph nodes <15 (Fig. 2f) and without chemotherapy (Fig. 2g)), the hazard pattern was more prominent, and the hazard curve was steeper.

Table 1 Univariate survival analysis of clinic–pathologic variables in 1,222 cases of gastric cancer patients

Variable	*n* (%)	Log-rank x^2 value	*P* value
Gender		1.821	0.177
Male	823 (67.3)		
Female	399 (32.7)		
Age (years)		17.963	<0.001*
≤40	146 (11.9)		
41–60	584 (47.8)		
>61	492 (40.3)		
Tumor location		104.259	<0.001*
Proximal	542 (44.4)		
Middle	158 (12.9)		
Distal	479 (39.2)		
Two-thirds or more	43 (3.5)		
Tumor size (cm)		79.985	<0.001*
≤5.0	736 (60.2)		
>5.0	486 (39.8)		
Histological grade		13.181	<0.001*
Well-/moderately differentiated adenocarcinoma	463 (37.9)		
Poorly differentiated/undifferentiated adenocarcinoma/signet ring cell carcinoma/mucinous adenocarcinoma	759 (62.1)		
Lymphatic/venous invasion		65.022	<0.001*
No	1133 (92.7)		
Yes	89 (7.3)		
Depth of invasion (7th edition)		219.905	<0.001*
T1	111 (9.1)		
T2	161 (13.2)		
T3	237 (19.4)		
T4a	609 (49.8)		
T4b	104 (8.5)		
Nodal status (7th edition)		254.231	<0.001*
N0	426 (34.9)		
N1	254 (20.8)		
N2	296 (24.2)		
N3	246 (20.1)		
Retrieved lymph nodes		38.521	<0.001*
<15	681 (55.7)		
≥15	541 (44.3)		
Chemotherapy		50.885	<0.001*
Yes	701 (57.4)		
No	521 (42.6)		

* Statistically significant at $P<0.05$

Discussion

To the best of our knowledge, this study is the first retrospective analysis of the postoperative recurrence pattern of gastric cancer. This pattern is similar to the double-peaked recurrence pattern of breast cancer, but with some differences. The occurrence time for the early peak in gastric cancer is the same as that in breast cancer. However, the late recurrence occurs later in gastric cancer and appears as a rising trend rather than a peak within 10 years after surgery [6]. In our attempt to explain this phenomenon, we believed that the hypothesis of tumor dormancy might satisfactorily fit our findings [5, 6, 8, 9]. This hypothesis assumes the presence of micrometastatic foci in various biological steady states in the preclinical stage, most of which do not progress to tumor growth. However, surgery may perturb this orderly and stable process and stimulate the dormant micrometastatic foci to grow, which results in the sudden acceleration of the metastatic process and eventually leads to recurrence [10]. This phenomenon may account for the early recurrence peak.

Table 2 Multivariate survival analysis results

Variable	Wald	*P*	HR	95 % CI
Age	5.878	0.015*	1.009	1.002–1.016
Tumor location	9.297	0.002*	0.879	0.808–0.955
Tumor size	18.044	<0.001*	1.383	1.191–1.606
Histological grade	6.270	0.012*	1.231	1.046–1.449
Lymphatic/venous invasion	34.638	<0.001*	2.125	1.653–2.732
Depth of invasion	78.153	<0.001*	1.488	1.362–1.625
Nodal status	160.590	<0.001*	1.634	1.514–1.763
Retrieved lymph nodes	54.416	<0.001*	0.537	0.456–0.634
Chemotherapy	35.415	<0.001*	0.622	0.532–0.727

CI confidence interval

* Statistically significant at $P<0.05$

According to the tumor dormancy hypothesis, surgery may accelerate metastatic development by triggering tumor growth. However, we cannot deny the role of surgery in the treatment of the primary tumor. Indeed, surgery is the main treatment for operable gastric cancer [11]. Therefore, we should learn more regarding the biological behavior of gastric cancer from the results of our findings to help enlighten us about treatment. In a further subgroup analysis, we found that the recurrence rate was closely related to both the surgery and the chemotherapy after surgery. For surgery, if there are <15 retrieved lymph nodes, the curve of recurrence was steeper, indicating that the patients were more likely to relapse. This finding supports the NCCN guidelines concerning gastric cancer surgery, which state that the number of retrieved lymph nodes should be ≥15, which is consistent with other reports [12]. Therefore, we should be attentive to the quality of the surgery. For chemotherapy, the curves of the patients who received

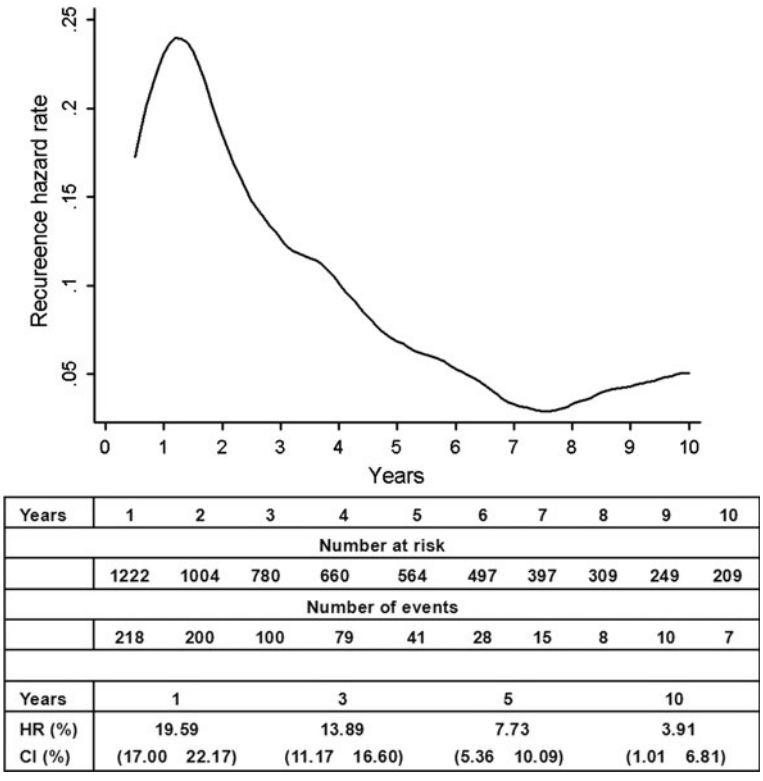

Fig. 1 Annual recurrence hazard rate for 1222 gastric cancer patients. *HR* hazard rate, *CI* confidence interval

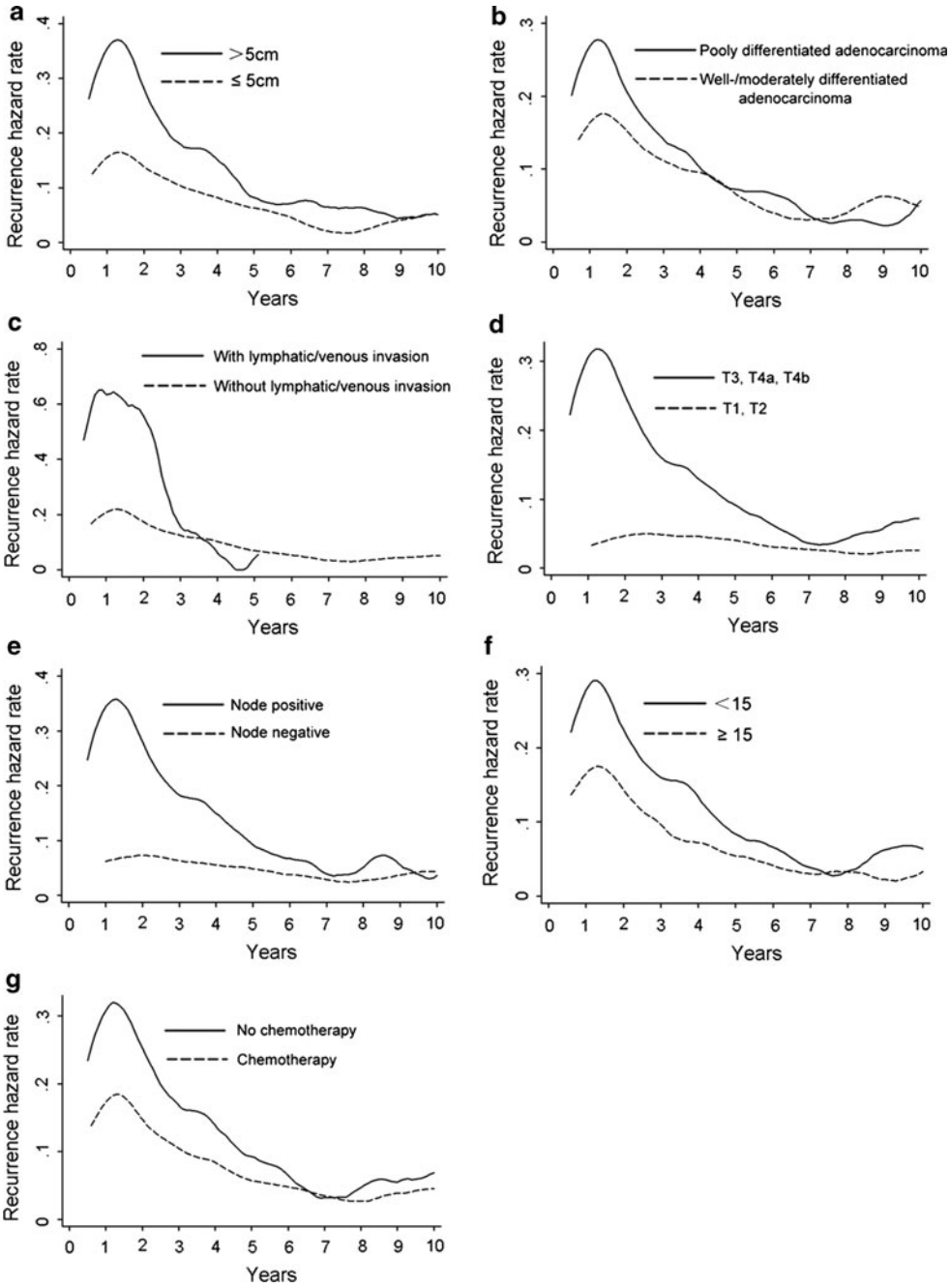

Fig. 2 Annual recurrence hazard rate for 1222 gastric cancer patients by tumor size, histological grade, lymphatic/venous invasion, depth of invasion, nodal status, number of retrieved lymph nodes and chemotherapy **a** Tumor diameter ≤5 cm versus tumor diameter>5 cm **b** Well-/moderately differentiated adenocarcinoma versus poorly differentiated/undifferentiated adenocarcinoma/signet ring cell carcinoma/mucinous adenocarcinoma **c** Lymphatic/venous invasion negative versus lymphatic/venous invasion positive **d** T1 and T2 versus T3, T4a, T4b **e** Node negative versus node positive **f** The number of retrieved lymph nodes ≥15 versus <15 **g** Chemotherapy versus no chemotherapy. *HR,* hazard rate; *CI,* confidence interval

chemotherapy were flatter, indicating that chemotherapy after surgery can reduce the hazard rate. This finding further emphasizes the need for chemotherapy [13].

Furthermore, the subgroup analysis revealed some high-risk factors, including a larger tumor size, poorly differentiated/undifferentiated adenocarcinoma, lymphatic/venous invasion, the T3 and T4 stage and a node-positive status. The curves of the patients with these factors were steeper, indicating that these patients were more likely to relapse. The results of a multivariate Cox proportional hazards regression analysis also support this finding. These findings are similar to those of several other studies [3, 14]. Therefore, chemotherapy or other treatments after surgery are more important for patients who present these high-risk factors.

Furthermore, we also found that the first recurrence peak nearly covered the 3 years after surgery. However, chemotherapy cannot be used continuously for 3 years to cover the first recurrence peak because of its side-effects; both the NCCN guidelines and the Japanese gastric cancer association (JGCA) suggest that the length of chemotherapy should not exceed 1 year. Therefore, we must find additional

treatments to further reduce the risk of recurrence. Immunotherapy is a potentially valuable treatment that can reduce the risk of recurrence [15].

Finally, using the time-varying pattern of the recurrence risk for gastric cancer, we may be able to formulate individual treatments and follow-up.

Acknowledgments This work was supported by grants from the Science and Technology Projects of Guangdong Province (2011B06 1300052) and the National Nature Science Foundation of China (30972882, 81272341).

Conflict of interest None.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69–90. doi:10.3322/caac.20107.
2. Choi JY, Ha TK, Kwon SJ. Clinicopathologic characteristics of gastric cancer patients according to the timing of the recurrence after curative surgery. J Gastric Cancer. 2011;11(1):46–54. doi:10.5230/jgc.2011.11.1.46.
3. Shiraishi N, Inomata M, Osawa N, Yasuda K, Adachi Y, Kitano S. Early and late recurrence after gastrectomy for gastric carcinoma. Univariate and multivariate analyses. Cancer. 2000;89(2):255–61. doi:10.1002/1097-0142.
4. Saphner T, Tormey DC, Gray R. Annual hazard rates of recurrence for breast cancer after primary therapy. J Clin Oncol. 1996;14(10):2738–46.
5. Yin W, Di G, Zhou L, Lu J, Liu G, Wu J, et al. Time-varying pattern of recurrence risk for Chinese breast cancer patients. Breast Cancer Res Treat. 2009;114(3):527–35. doi:10.1007/s10549-008-0022-5.
6. Demicheli R, Abbattista A, Miceli R, Valagussa P, Bonadonna G. Time distribution of the recurrence risk for breast cancer patients undergoing mastectomy: further support about the concept of tumor dormancy. Breast Cancer Res Treat. 1996;41(2):177–85.
7. Ramlau-Hansen H. Smoothing counting process intensities by means of kernel functions. Ann Stat. 1983;11:453–66.
8. Holmgren L, O'Reilly MS, Folkman J. Dormancy of micrometastases: balanced proliferation and apoptosis in the presence of angiogenesis suppression. Nat Med. 1995;1(2):149–53.
9. Uhr JW, Tucker T, May RD, Siu H, Vitetta ES. Cancer dormancy: studies of the murine BCL1 lymphoma. Cancer Res. 1991;51(18 Suppl):5045s–53s.
10. Demicheli R. Tumour dormancy: findings and hypotheses from clinical research on breast cancer. Semin Cancer Biol. 2001;11(4):297–306. doi:10.1006/scbi.2001.0385.
11. Wang W, Li YF, Sun XW, Chen YB, Li W, Xu DZ, et al. Prognosis of 980 patients with gastric cancer after surgical resection. Chin J Cancer. 2010;29(11):923–30.
12. Schwarz RE, Smith DD. Clinical impact of lymphadenectomy extent in resectable gastric cancer of advanced stage. Ann Surg Oncol. 2007;14(2):317–28. doi:10.1245/s10434-006-9218-2.
13. Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet. 2012;379(9813):315–21. doi:10.1016/S0140-6736(11)61873-4.
14. Yokota T, Saito T, Teshima S, Yamada Y, Iwamoto K, Takahashi M, et al. Early and late recurrences after gastrectomy for gastric cancer: a multiple logistic regression analysis. Ups J Med Sci. 2002;107(1):17–22.
15. Kim JP, Kwon OJ, Oh ST, Yang HK. Results of surgery on 6,589 gastric cancer patients and immunochemosurgery as the best treatment of advanced gastric cancer. Ann Surg. 1992;216(3):269–78. discussion 78–9.