

Surgical Outcome of Synchronous Second Primary Cancer in Patients with Gastric Cancer

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Purpose: In order to improve the likelihood of curative and safe gastric surgery, this study investigated the clinical features and surgical outcomes of gastric cancer with a synchronous cancer. **Patients and Methods:** The clinicopathological data of 10,090 gastric cancer patients at Samsung Medical Center from September 1994 to December 2006 were retrospectively analyzed. Of them, 90 patients with gastric cancer and a synchronous second primary cancer underwent simultaneous surgery for gastric cancer and second primary cancer. The clinicopathological characteristics of the patients, surgical outcome, and prognosis were examined. **Results:** The most common synchronous second primary cancer was colorectal cancer (37 patients), followed by hepatocellular carcinoma (13 patients), renal cell carcinoma (11 patients), and pancreatic carcinoma (5 patients). The incidence of a second primary cancer in the gastric cancer patients was higher than the incidence in the general population. Stage I gastric cancer patients had more synchronous cancers than stage II patients (59 vs. 31). Postoperative complications were encountered in 7 patients. Four patients underwent reoperation. Two patients died from hepatic failure and leakage of esophagojejunal anastomosis. The 5-year survival rate of stage I and II gastric cancer was 61% and 39%, respectively. **Conclusion:** Since gastric cancer patients with a synchronous second primary cancer are not rare, the possibility of synchronous cancers in gastric cancer patients should be considered. The prognosis of early stage gastric cancer patients with a synchronous second primary cancer was influenced more by the presence of the second primary cancer than by the gastric cancer itself.

Key Words: Second primary cancer, gastric cancer

INTRODUCTION

Although the number of cancer deaths has declined, gastric cancer is the one of the most common causes of cancer death in Korea.¹ Recently, the prognosis of gastric cancer has improved due to early diagnosis, enhancement of surgical techniques, and the development of new chemotherapeutic agents,²⁻⁵ but gastric cancer remains the second most common cause of death in Korea. The incidence of gastric cancer with a second primary cancer is growing along with the increasing age of gastric cancer patients.⁶ The prognosis of early gastric cancer is excellent, and it can be treated with curative resection if another incurable cancer is not present. A second primary cancer may influence the prognosis of gastric cancer, making it important to recognize the clinicopathological characteristics and outcome of gastric cancer with a synchronous second primary cancer.⁶⁻⁸ There are no reports of the surgical results of combined surgery for gastric cancer and a synchronous second primary cancer. Moreover, there are only a few discussions of the features related to gastric cancer with a synchronous and metachronous second primary cancer.⁶⁻¹² The best simultaneous treatment for gastric cancer with a synchronous second primary cancer has not been determined definitively. This study examined the clinicopathological significance, surgical outcome, and prognosis of gastric cancer patients with a synchronous second primary cancer who underwent a simultaneous surgical resection.

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PATIENTS AND METHODS

This study retrospectively analyzed 10,090 patients who underwent gastric surgery for gastric cancer at the Department of Surgery, Samsung Medical Center, from September 1994 to December 2006. Among the 10,090 patients, we analyzed those who had undergone a gastrectomy and combined surgery for a synchronous second primary cancer. Synchronous second primary cancers were defined as cancer diagnosed in organs other than the stomach, at the same time or within six months before the diagnosis of the first primary cancer. In total, 96 patients were identified with gastric cancer and a synchronous second primary cancer. Abdominopelvic computed tomography, esophagogastroduodenoscopy, and double contrast barium study were performed routinely before the operation. Six patients could not undergo a gastrectomy because of the unresectability of the cancer. Ninety gastrectomies and surgeries on the second primary cancer were performed within one month of diagnosis. The synchronous second primary cancers were confirmed pathologically by surgery or a preoperative biopsy. Clinicopathological characteristics including age, gender, operation, histology, stage, and complications were reviewed.

Statistical analysis

The data were analyzed using the Statistical Package for Social Science (SPSS) version 12.0 for Windows (SPSS, Inc, Chicago, IL). The survival curve was calculated using the Kaplan-Meier

procedure. A p value <0.05 was considered significant.

RESULTS

Clinicopathological features of all gastric cancer patients

Among the 10,090 gastric cancer patients, 96 (1.0%) had a synchronous cancer on the other organs. Of these 96 patients, 6 could not undergo a gastrectomy due to the unresectability of their cancer. Overall, 90 patients underwent a gastrectomy combined with surgery for a synchronous second primary cancer. Table 1 shows their clinicopathological characteristics. Of the 90 patients, 75 were male (83.3%) and 47 (52.2%) had early gastric cancer. Stage I gastric cancer (59 patients, 65.6%) was the most common stage (Table 1).

Site and incidence of synchronous second primary cancer

The most common site of the second primary cancer was the colorectum, followed by the liver, kidney, and pancreas. Fig. 1 shows the incidence of the second primary cancer in gastric cancer patients who underwent gastrectomy at our hospital along with the incidence of cancer in the general population in Korea for comparison¹³. Patients with gastric cancer had a higher incidence of colorectum, liver, kidney, and pancreas cancer. Colorectal cancer was the most common

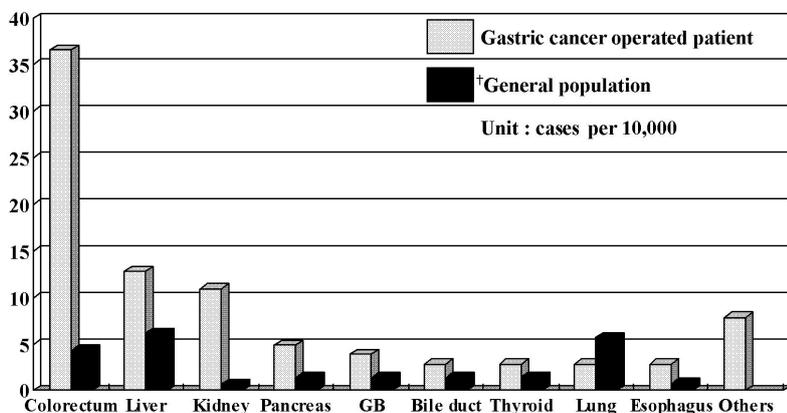


Fig. 1. Incidence of second primary cancer and incidence. *Other: duodenum, breast, prostate, ureter, appendix, melanoma, mucoepidermoid tumor, cervix. †Data for cancer incidence was based on annual report of the Korea Central Cancer Registry 2001.

Table 1. Clinicopathologic Characteristics of Patients with Gastric Cancer with and without Synchronous Second Primary Cancer

Factors	Gastric cancer with SPC n = 90 (%)	Gastric cancer without SPC n = 10,000 (%)
Sex		
Male	75 (83.3)	6,625 (66.3)
Female	15 (16.7)	3,375 (33.8)
Age (yrs)	60.8 ± 10.3	55.6 ± 12.0
Depth of invasion		
T1 (EGC)	47 (52.2)	4,539 (45.4)
T2 - 4 (AGC)	43 (47.8)	5,026 (50.2)
Unknown	0 (0.0)	435 (4.4)
Differentiation		
Differentiated	56 (62.2)	4,350 (43.5)
Undifferentiated	33 (36.7)	5,404 (54.0)
Others	1 (1.1)	37 (0.4)
Unknown	0 (0.0)	209 (2.1)
Stage		
I	59 (65.6)	4,785 (47.9)
II	12 (13.3)	1,151 (11.5)
III	12 (13.3)	1,069 (10.7)
IV	7 (7.8)	1,736 (17.4)
Unknown	0 (0.0)	1,259 (12.6)
Curability		
R0	88 (97.8)	8,860 (88.6)
R1	2 (2.2)	449 (4.5)
R2	0 (0.0)	691 (6.9)

EGC, early gastric cancer; AGC, advanced gastric cancer; SPC, second primary cancer; Others, hepatoid adenocarcinoma, adenosquamous carcinoma, anaplastic carcinoma, lymphoepithelioma like carcinoma, small cell carcinoma, composite adenocarcinoma-neuroendocrine carcinoma.

synchronous cancer in gastric cancer. While other studies^{6,7} reported lung cancer to be most common, followed by colorectal cancer, hepatocellular carcinoma was the second most common cancer in this study. During the follow-up period, a newly developed cancer was identified in three patients. One patient, who had colon cancer, previously underwent a pancreaticoduodenectomy for duodenal cancer followed by left hemicolectomy. The other patient, who underwent a right hemicolectomy due to an ascending colon cancer, was diagnosed with renal cell carcinoma, but could not undergo surgery because the tumor was unresectable. The final patient, who was diagnosed

with ascending colon cancer, had bladder cancer and underwent a transurethral resection of the bladder.

Surgery for the synchronous second primary cancer

Table 2 shows the gastric surgical procedures for the combined gastric cancer and synchronous second primary cancer. All patients underwent gastric cancer surgery. A distal gastrectomy (58, 64.4%) was most common, followed by a total gastrectomy (28, 31.1%), pancreaticoduodenectomy (2, 2.2%), proximal gastrectomy (1, 1.1%), and a local excision (1, 1.1%). Postoperative complica-

Table 2. Classification of Gastric Cancer Operations and Combined Operations for Synchronous Second Primary Cancer

		Total gastrectomy	Distal gastrectomy	Proximal gastrectomy	Others
Colorectum	Anterior resection	1	3	0	0
	Hartmann's operation	0	4	0	0
	Low anterior resection	4	3	1	0
	Miles' operation	0	1	0	0
	Right hemicolectomy	1	14	0	0
	TEM	1	1	0	0
	Total colectomy	1	0	0	1
Liver	Enucleation	1	2	0	0
	Intraoperative radiofrequency ablation	2	1	0	0
	Lobectomy	3	2	0	0
	Sectionectomy	1	3	0	0
Gallbladder, Pancreas	Cholecystectomy	1	2	0	0
	Pancreaticoduodenectomy	1	3	0	2
	Distal pancreatectomy	1	1	0	0
Kidney	Radical nephrectomy	4	7	0	0
Breast	Breast conservation surgery	1	0	0	0
Thyroid	Total thyroidectomy	0	3	0	0
Lung	Lobectomy	0	3	0	0
Esophagus	Esophagectomy	3	0	0	0
Prostate	TURP	0	1	0	0
Ureter	Nephroureterectomy	0	1	0	0
Neck	Radical neck dissection	1	0	0	0
Melanoma	SNB & wide excision	0	1	0	0
Cervix	TAH & BSO	0	1	0	0

Others, local excision, pancreaticoduodenectomy; TEM, transanal endoscopic microsurgery; TURP, transurethral resection of the prostate; SNB, sentinel node biopsy; TAH & BSO, total abdominal hysterectomies with bilateral salpingo-oophorectomy.

tions were encountered in seven patients including hepatic failure (2 patients), pneumonia (1 patient), wound dehiscence (1 patient), subphrenic abscess (1 patient), leakage of anastomosis (1 patient), and mechanical ileus (1 patient). The patient with hepatic failure underwent a shunt operation to control the ascites and survived. Two patients died of hepatic failure and leakage caused by esophagojejunal anastomosis.

Site distribution of the second primary cancer and 5-year survival rate

Table 3 shows the site distribution of second

primary cancers in patients with gastric cancer, the number of dead patients, and the 5-year survival rate according to the stage of gastric cancer. The 5-year survival rates of stage I and II gastric cancer were 61% and 39%, respectively, which are less than that of patients with gastric cancer without a second primary cancer.¹⁴ The 5-year survival rate of patients with colorectal cancer and a gastric cancer was 66%, which is higher than that of patients with other cancers. However all patients with pancreas cancer and gastric cancer died. The synchronous second primary cancer adversely affected the survival of early stage gastric cancer patients.

Table 3. Site Distribution of Synchronous Second Primary Cancers in Patients with Gastric Cancer and 5-Year Survival Rate

Site	Stage of gastric cancer				5 YSR (%)
	I	II	III	IV	
Colorectum	27 (5)	2 (0)	5 (2)	3 (2)	66
Liver	7 (4)	3 (3)	2 (1)	1 (1)	43
Kidney	6 (2)	3 (2)	1 (1)	1 (1)	24
Pancreas	4 (4)	1 (1)	0 (0)	0 (0)	0
Others	15 (4)	3 (1)	4 (2)	2 (1)	60
5 YSR (%)	61	39	30	0	

Others: GB (1), bile duct (2), lung (3), appendix (1), mucoepidermoid tumor (1).

Parenthesis: number of patients who died.

YSR, year survival rate.

DISCUSSION

The incidence of gastric cancer with a synchronous second primary cancer varies from 2.0% to 10.9%.⁶⁻⁸ Our incidence (1.0%) was lower than that of other reports. However, this lower incidence might be due to the fact that this study analyzed patients who had undergone a gastrectomy and combined surgery for a synchronous second primary cancer and examined the prognosis of these patients.

The detection of early gastric cancer is better due to the aid of radiologic diagnostic tools, mass screening, interest in health, and increasing patient age.^{2,4} Therefore, there has been an increase in the rate of detection of synchronous second primary cancers. The prognosis of early gastric cancer is more favorable than advanced gastric cancer, but there are few reports on how to treat or improve the survival of patients with a synchronous second primary cancer,⁶⁻¹² which remains a key challenge.

Colorectal cancer is diagnosed most commonly in patients with gastric cancer.^{6-9,12} We found that colorectal cancer was the most common synchronous cancer in gastric cancer. The incidence of colorectal cancer is increasing rapidly in Korea,¹ which might affect the detection of a synchronous colon cancer. Lung cancer was also quite prevalent. However, we encountered only three lung cancer patients because only synchronous second primary cancers were investigated and lung cancer is usually detected metachronously.⁷ Colorectal and

gastric cancer might be closely related, and there are data to support this relationship. Gastric cancer is the most common extra-colonic cancer associated with hereditary non-polyposis colorectal cancer (HNPCC) syndrome.¹⁵ Familial gastric cancer is independently associated with the presence of a mismatch repair gene has been identified in gastric cancer as well as in colorectal cancer.^{16,17} However, the basic mechanism for carcinogenesis is unknown. In this report, the survival of patients with colorectal cancer and gastric cancer was higher than that of the other cancers.

Hepatocellular carcinoma (HCC) is a very common malignancy in Korea,¹ but the co-existence of HCC and gastric cancer is rare.¹⁸ A differential diagnosis of primary HCC should be made because the liver is a metastatic site of gastric cancer. Therefore, a definitive management strategy for synchronous HCC and gastric cancer has not been established. Some studies have reported that synchronous cancer, including gastric cancer, has no effect on postoperative survival in patients with HCC when a simultaneous resection is performed.^{18,19} Although a combined resection might be possible, the surgical options are more restricted than those for other malignancies because HCC patients also have liver cirrhosis and limited liver function.²⁰ We encountered five early gastric cancer cases and eight advanced gastric cancer cases with HCC. Only one patient with early gastric cancer who underwent a subtotal gastrectomy and

sectionectomy of the liver died from postoperative hepatic failure. Minimal invasive surgery should be considered when gastric cancer is identified as early stage in patients with HCC. Since the risk of lymph node metastasis is low, a lymph node dissection is not performed routinely, which later causes massive lymphorrhea, postoperative morbidity, and death.²¹ The most common cause of death in patients with HCC and gastric cancer is the recurrence of HCC.^{18,19}

The incidence of gastric cancer with renal cell carcinoma is quite low.^{22,23} Moreover, synchronous surgery of gastric cancer and renal cell carcinoma is extremely rare.^{6,7} On the other hand, patients with renal cell carcinoma have a significantly higher risk of other subsequent primary malignancies.^{6,7,24} A curative resection was performed on 11 patients diagnosed with gastric cancer combined with renal cell carcinoma in this study. One of them died from postoperative morbidity because of anastomosis leakage. During the postoperative follow-up period, renal cell carcinoma and gastric cancers recurred in six patients, five of whom died.

The incidence of a second primary gastric cancer is increasing more in males than females, and tends to be higher in elderly patients.^{6,7} The incidence of synchronous cancer in early stage gastric cancer is higher than that in advanced stage.²⁵ This finding is associated with a trend in recent gastric cancer epidemiology and the features of gastric cancer in Korea.

The prognosis of gastric cancer is not as good as expected. However, the prognosis of early gastric cancer has been improved.¹⁴ In this study, the 5-year survival rate of stage I and II gastric cancer was 61% and 39%, respectively. Therefore, the presence of the second primary cancer has a more adverse effect on the prognosis of early stage gastric cancer with a synchronous second primary cancer than the gastric cancer itself.

In conclusion, the incidence of early gastric cancer has increased recently. Surgeons need to be aware of the possibility of a synchronous second primary cancer with gastric cancer because the prognosis of early gastric cancer is adversely affected by the presence of a second primary cancer.

REFERENCES

1. Bae JM, Jung KW, Won YJ. Estimation of cancer deaths in Korea for the upcoming years. *J Korean Med Sci* 2002;17:611-5.
2. Kim YS, Park HA, Kim BS, Yook JH, Lee MS. Efficacy of screening for gastric cancer in a Korean adult population: a case-control study. *J Korean Med Sci* 2000;15:510-5.
3. Sastre J, Garcia-Saenz JA, Diaz-Rubio E. Chemotherapy for gastric cancer. *World J Gastroenterol* 2006;12:204-13.
4. Yoshida S, Kozu T, Gotoda T, Saito D. Detection and treatment of early cancer in high-risk populations. *Best Pract Res Clin Gastroenterol* 2006;20:745-65.
5. Zhang XF, Huang CM, Lu HS, Wu XY, Wang C, Guang GX, et al. Surgical treatment and prognosis of gastric cancer in 2,613 patients. *World J Gastroenterol* 2004;10:3405-8.
6. Lee JH, Bae JS, Ryu KW, Lee JS, Park SR, Kim CG, et al. Gastric cancer patients at high-risk of having synchronous cancer. *World J Gastroenterol* 2006;12:2588-92.
7. Ikeda Y, Saku M, Kawanaka H, Nonaka M, Yoshida K. Features of second primary cancer in patients with gastric cancer. *Oncology* 2003;65:113-7.
8. Yoshino K, Asanuma F, Hanatani Y, Otani Y, Kumai K, Ishibiki K. Multiple primary cancers in the stomach and another organ: frequency and the effects on prognosis. *Jpn J Clin Oncol* 1985;15 Suppl 1:183-90.
9. Cheng HY, Chu CH, Chang WH, Hsu TC, Lin SC, Liu CC, et al. Clinical analysis of multiple primary malignancies in the digestive system: a hospital-based study. *World J Gastroenterol* 2005;11:4215-9.
10. Furukawa H, Hiratsuka M, Iwanaga T, Imaoka S, Kabuto T, Ishikawa O, et al. Treatments for second malignancies after gastrectomy for stomach cancer. *Hepatogastroenterology* 1996;43:194-8.
11. Ikeguchi M, Ohfuji S, Oka A, Tsujitani S, Maeda M, Kaibara N. Synchronous and metachronous primary malignancies in organs other than the stomach in patients with early gastric cancer. *Hepatogastroenterology* 1995;42:672-6.
12. Nio Y, Hirahara N, Minari Y, Sasaki S, Takamura M, Sato Y, et al. Second malignancies after a gastrectomy for gastric cancers: the effects of adjuvant therapies. *Anticancer Res* 1999;19:3591-9.
13. Lee HJ, Yang HK, Ahn YO. Gastric cancer in Korea. *Gastric Cancer* 2002;5:177-82.
14. Kim JP, Hur YS, Yang HK. Lymph node metastasis as a significant prognostic factor in early gastric cancer: analysis of 1,136 early gastric cancers. *Ann Surg Oncol* 1995;2:308-13.
15. Gylling A, Abdel-Rahman WM, Juhola M, Nuorva K, Hautala E, Jarvinen HJ, et al. Is gastric cancer part of the tumor spectrum of hereditary non-polyposis colorectal cancer? A molecular genetic study. *Gut* 2007;56:926-33.

16. Keller G, Grimm V, Vogelsang H, Bischoff P, Mueller J, Siewert JR, et al. Analysis for microsatellite instability and mutations of the DNA mismatch repair gene hMLH1 in familial gastric cancer. *Int J Cancer* 1996; 68:571-6.
17. Kim JC, Kim HC, Roh SA, Koo KH, Lee DH, Yu CS, et al. hMLH1 and hMSH2 mutations in families with familial clustering of gastric cancer and hereditary non-polyposis colorectal cancer. *Cancer Detect Prev* 2001;25:503-10.
18. Koide N, Hanazaki K, Fujimori Y, Igarashi J, Kajikawa S, Adachi W, et al. Synchronous gastric cancer associated with hepatocellular carcinoma: a study of 10 patients. *Hepatogastroenterology* 1999;46:3008-14.
19. Shimada M, Takenaka K, Fujiwara Y, Gion T, Shirabe K, Nishizaki T, et al. Characteristics of hepatocellular carcinoma associated with extrahepatic primary malignancies in southern Japan. *Am J Gastroenterol* 1996;91:754-8.
20. Shuto T, Hirohashi K, Kubo S, Tanaka H, Tsukamoto T, Yamamoto T, et al. Changes and results of surgical strategies for hepatocellular carcinoma: results of a 15-year study on 452 consecutive patients. *Surg Today* 1998;28:1124-9.
21. Isozaki H, Okajima K, Ichinona T, Fujii K, Nomura E, Izumi N. Surgery for gastric cancer in patients with cirrhosis. *Surg Today* 1997;27:17-21.
22. Murakami S, Yashuda S, Nakamura T, Mishima Y, Iida H, Okano H, et al. A case of renal cell carcinoma with metastasis to the thyroid gland and concomitant early gastric cancer. *Surg Today* 1993;23:153-8.
23. Uemura T, Kurita A, Nishimura R, Ishizaki M, Takashima S. Solitary pancreatic metastasis from renal cell carcinoma concomitant with early gastric cancer 17 years after nephrectomy: report of a case. *Surg Today* 2003;33:395-8.
24. Beisland C, Talleraas O, Bakke A, Norstein J. Multiple primary malignancies in patients with renal cell carcinoma: a national population-based cohort study. *BJU Int* 2006;97:698-702.
25. Urano Y, Itoyama S, Fukushima T, Kitamura S, Mori H, Baba K, et al. Multiple primary cancers in autopsy cases of Tokyo University Hospital (1883-1982) and in Japan Autopsy Annuals (1974-1982). *Jpn J Clin Oncol* 1985;15 Suppl 1:271-9.