Synchronous Colon Primaries Have the Same Prognosis as Solitary Colon Cancers

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PURPOSE: This study was designed to determine the prognosis of patients with synchronous colon primary tumors. METHODS: An 18-year, multi-institutional database of 4,878 colon cancer patients was reviewed, and patients with synchronous tumors were identified. Survival for each group was calculated by the Kaplan-Meier method and compared using log-rank analysis. RESULTS: There were 160 patients (3.3 percent) with 339 synchronous tumors. Eight percent of these patients had more than two tumors at the time of diagnosis. TNM staging of all synchronous tumors was 12 percent Stage 0, 41 percent Stage I, 21 percent Stage II, 16 percent Stage III, and 7 percent Stage IV. Based on highest stage lesion, 1 percent of patients were at Stage 0, 28 percent Stage I, 33 percent Stage II, 25 percent Stage III, and 11 percent Stage IV. Disease-specific five-year survival by highest stage was 87 percent for Stage O or I, 69 percent for Stage II, 50 percent for Stage III, and 14 percent for Stage IV (all differences significant by log-rank test). These "highest stage" survivals for patients with synchronous tumors were not significantly different from survival of patients with same stage solitary tumors in our database or from survival of patients with solitary colon cancer in national tumor databases. CONCLUSION: For patients with synchronous colon cancers, survival is the same as for patients with solitary colon tumors on a stage-for-stage basis, when highest stage synchronous tumor is considered. [Key words: Colon cancer; Synchronous; Solitary; Prognosis]

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It has been more than a century since Czerny,[1] Fenger,[2] and Billroth[3] reported the first cases of multiple synchronous colorectal carcinomas, yet much controversy regarding this condition still exists. The reported prevalence of synchronous colon cancer varies from 2 to 9 percent.[4–20] Much of this variability is related to differences in patient populations, time periods studied, and diagnostic criteria used.[4–34]

Prognosis of patients with synchronous colon tumors has also been reported in the literature.[21–34] Whereas some studies have found no difference in long-term survival,[26, 27, 30, 32, 34] others have reported worse prognosis,[23, 28, 29] and still others have reported a better outcome in patients with synchronous primary colon tumors compared with patients with solitary tumors.[24, 31] Unfortunately, most studies lack long-term follow-up or sufficient numbers of patients to give statistical power to survival data. In fact, prognosis of patients with synchronous colon primaries is essentially unknown by current staging criteria.[35] The purpose of this study was to determine prognosis of synchronous colon primaries from a large series of patients and to compare it with prognosis of patients with a single colon primary during the same time period, using the American Joint Committee on Cancer tumor, nodes, and metastasis (TNM) staging criteria.

METHODS

All patients who underwent resection of synchronous colon primaries between January 1, 1976, and December 31, 1993, were identified from tumor registries of four Portland, Oregon area hospitals, including a university hospital (Oregon Health Sciences University), two private hospitals (St. Vincent Hospital and Providence Hospital), and a Veterans Affairs hospital (Portland VA Medical Center). All synchronous cancers in the database met the criteria of Warren and Gates[36] and Moertel *et al.*[37]: 1) two distinct colonic malignancies separated by a segment of normal colon mucosa and bowel wall; and 2) neither tumor represented an extension or a metastasis of the other. Patients with a diagnosis of inflammatory bowel disease or familial polyposis were excluded from the study. All patients with a solitary colon primary tumor diagnosed and treated during the same time period were also identified from the database and served as the control group in this study.

Location and histology of all synchronous and solitary tumors were reviewed. All tumors before 1988

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had been staged under the Surveillance, Epidemiology, and End Results staging system and since 1988 under the American Joint Committee on Cancer TNM staging system.[35] For the purpose of this study, all tumors were staged according to the TNM system or by the Surveillance, Epidemiology, and End Results equivalent ("*in situ*" equal to Stage 0, "localized" equal to Stage I, "regional/direct extension" equal to Stage II, "regional/nodes" equal to Stage III, and "distant" equal to Stage IV). For synchronous cases, the tumor with the highest TNM stage was considered as the "index" cancer in survival calculations. Disease-specific survival rates for patients with both synchronous and single colon primary tumors were calculated by the Kaplan-Meier method, and survival curves were compared using the log-rank test.

RESULTS

During the 18-year study period, 4,878 patients with colon cancer were entered into the multi-institutional tumor registry. Of these, there were 4,718 patients (96.7 percent) with a single colon primary and 160 patients (3.3 percent) with 339 synchronous colon primaries. Age and male/female distribution at time of presentation for patients with single and synchronous tumors is shown in Figure 1. Although there was no difference in male/female distribution, patients with synchronous primaries were older than patients with single colon primaries, with mean ages of 71.2 ± 10.2 years and 67.8 ± 11.7 years, respectively ($P < 0.001$).

One hundred forty-seven (91.8 percent) patients with synchronous primaries had two tumors at time of diagnosis, nine (5.6 percent) had three tumors, two (1.3 percent) had four tumors, and two (1.3 percent) had five or more. Histologies of all single and synchronous colon primaries are shown in Table 1. Adenocarcinoma either arising *de novo* or from a polyp/adenoma was the most common histology for both single and synchronous colon tumors, representing 87.9 and 82.6 percent of all tumors, respectively. One hundred twenty-one of 160 patients (75.6 percent) with synchronous colon primaries had tumors of the same histology, and 39 (24.4 percent) had tumors of different histologies ($P < 0.001$).

Specific location of all synchronous colon primaries is shown in Figure 2. Most frequent location of all synchronous tumors was the sigmoid colon (24.8 percent) followed by the cecum (20.4 percent), transverse colon (13.6 percent), and ascending colon (13.0 percent). However, based on segmental location (Table 2), synchronous tumors were more frequent in the right colon (including appendix, cecum, ascending colon, and hepatic flexure) than were solitary cancers. Right colon was the site of 39.8 percent of synchronous tumors, compared with 31.7 percent for single colon tumors ($P < 0.005$). Single colon primaries were more frequent in the sigmoid colon, representing 33 percent of all tumors, compared with 24.8 percent for synchronous primaries ($P < 0.005$). In patients with synchronous tumors, 58 patients (36.3 percent) had tumors located in the same segment of the colon and 102 (63.8 percent) in a different segmental region ($P < 0.001$). Of patients with synchronous tumors in different segmental locations of the colon, 38 of 102 (37.2 percent) were in adjacent segments, but 64 of 102 (62.8 percent) were in completely separate segments ($P < 0.001$).

Distribution of single and synchronous colon primaries by stage is shown in Table 3. Seventy-one of 160 patients (44.4 percent) had synchronous tumors of the same stage, and 89 of 160 patients (55.6 percent) had tumors of different stages (P = not significant). Although the majority of all synchronous lesions were at an early stage (52.8 percent of Stages O or I compared with 21.2 percent of Stage II, 16.2 percent of Stage III, and 7.4 percent of Stage IV), when synchronous tumors are stratified according to the highest stage, most patients had more advanced disease (29.4 percent of Stages O or I compared with 32.5 percent of Stage II, 25 percent of Stage III, 11.3 percent of Stage IV). Comparing patients with single and synchronous colon primaries by highest stage, patients with solitary tumors were more frequently at

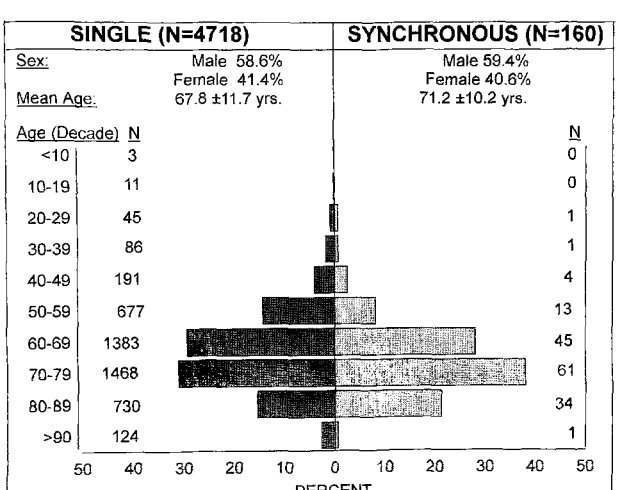

Figure 1. Demographic data for patients with solitary *vs.* synchronous colon tumors.

Table 1.
Histologies of Single and Synchronous Colon Primaries

Histology	Single (n = 4,718) (%)	Synchronous (n = 339) (%)	*P* value*
Carcinoma *in situ*	103 (2.2)	25 (7.4)	<0.001
Adenocarcinoma from polyp/adenoma	618 (13.1)	60 (17.7)	<0.05
Adenocarcinoma	3528 (74.8)	220 (64.9)	<0.001
Mucinous carcinoma	253 (5.4)	20 (5.9)	NS
Other	216 (4.6)	14 (4.1)	NS
Carcinoid	100 (2.1)	6 (1.8)	
Signet-ring	18 (0.4)	1 (0.3)	
Squamous-cell	8 (0.2)	1 (0.3)	
Lymphoma	5 (<0.1)	—	
Leiomyosarcoma	1 (<0.1)	1 (0.3)	
Melanoma	1 (<0.01)	—	
Transitional cell	1 (<0.01)	—	
Acinar	1 (<0.01)	—	
Miscellaneous	82 (1.7)	5 (1.4)	

NS = not significant.
* Chi-squared analysis.

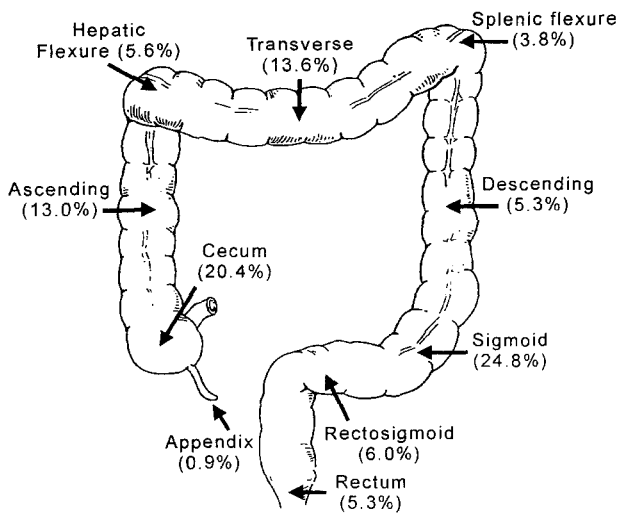

Figure 2. Specific location of 339 synchronous colon primaries in 160 patients.

an early stage (37.8 percent of single *vs.* 29.4 percent of synchronous; $P < 0.05$), and patients with synchronous tumors were more frequently at an advanced stage (58.7 percent of single *vs.* 68.8 percent of synchronous; $P < 0.05$).

Life table disease-specific survival at five years for synchronous colon primaries based on highest stage was 87 percent for Stages O or I, 67 percent for Stage II, 50 percent for Stage III, and 14 percent for Stage IV (Fig. 3). All five-year survival rates had a standard error less than 10 percent by life table method, and all survival curves were statistically different from one another by the log-rank test ($P < 0.05$). These survival figures are not significantly different from those of patients with same stage solitary colon cancers in our database or from published National Cancer Institute database for the Pacific Northwest[38] (Table 4).

DISCUSSION

Existence of synchronous carcinomas of the colon has been reported for many years, but there has been variability in the reported incidence, ranging from 2 to 9 percent.[4–19] Much of this variability has been because of differences in diagnostic criteria used, with some studies including metachronous tumors and benign synchronous polyps.[20] Using pathologic criteria of Warren and Gates[36] and Moertel *et al.*,[37] 160 patients with 339 synchronous colon primaries were identified from an 18-year multi-institutional tumor registry of 4,878 colon cancer patients, for an incidence of 3.3 percent. Of note, this incidence remained relatively constant during the time period studied.

Mean age of patients with synchronous colon primaries was found to be older than patients with single colon tumors (71.2 *vs.* 67.8 years, respectively). Some authors have also noted this finding,[16, 23, 29] although other investigators have reported that synchronous tumors were more frequent in younger patients.[17] Multiple colon tumors are found in younger patients with hereditary nonpolyposis colorectal carcinoma (HNPCC) syndromes.[39, 40] Although we do not know the incidence of such syndromes in our retrospective database, we would expect that at least some patients

Table 2.
Segmental Locations of Single and Synchronous Colon Primaries

Location	Single (n = 4,718) (%)	Synchronous (n = 339) (%)	*P* value*
Right colon†	1,495 (31.7)	135 (39.8)	<0.005
Transverse colon	414 (8.8)	46 (13.6)	<0.005
Descending colon‡	374 (7.9)	31 (9.1)	NS
Sigmoid/rectosigmoid	1,999 (42.3)	104 (30.7)	<0.001
Rectum	329 (7.0)	18 (5.3)	NS
Not specified	107 (2.3)	—	—

NS = not significant.
* Chi-squared analysis.
† Right colon includes appendix, cecum, ascending colon, and hepatic flexure.
‡ Descending colon includes splenic flexure and descending colon.

Table 3.
Distribution of Single and Synchronous Colon Primaries by Stage

Stage*	Single (n = 4,718) (%)	Synchronous All Tumors (n = 339) (%)	*P* Value†	Synchronous by Highest Stage (n = 160) (%)	*P* Value‡
0, I	1845 (37.8)	179 (52.8)	<0.001	46 (29.4)	<0.05
II	1085 (22.2)	72 (21.2)	NS	52 (32.5)	<0.005
III	825 (16.9)	55 (16.2)	NS	40 (25.0)	<0.01
IV	955 (19.6)	25 (7.4)	<0.001	18 (11.3)	<0.05
Not specified	168 (3.4)	8 (2.4)	NS	4 (2.5)	NS

NS = not significant.
* American Joint Committee on Cancer TNM stage or Surveillance, Epidemiology, and End Results equivalent.
† *P* value by chi-squared analysis comparing single with synchronous for all primaries.
‡ *P* value by chi-squared analysis comparing single with synchronous primaries by highest stage.

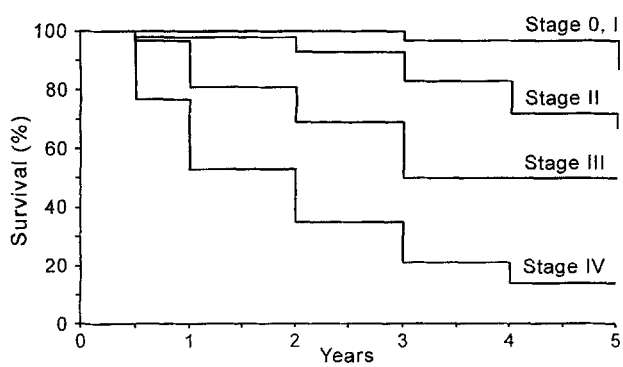

Figure 3. Disease-specific survival for patients with synchronous colon primaries by highest stage (n = 160). Calculation by Kaplan-Meier methods and comparison by the log-rank test.

Table 4.
Five-Year Survival for Single and Synchronous Colon Primaries (by Highest Stage)

Stage*	Synchronous by Highest Stage (n = 160) (%)	Single (n = 4,718) (%)	*P* value†	NCI (%)‡
0, I	87	83	NS	75–100
II	67	71	NS	50–75
III	50	53	NS	30–50
IV	14	9	NS	<10

NS = not significant.
* American Joint Committee on Cancer TNM stage or Surveillance, Epidemiology, and End Results equivalent.
† By log-rank test.
‡ Survival for colon cancer from the National Cancer Institute (NCI) for Pacific Northwest.[38]

with synchronous colon cancer are indeed cases of HNPCC. Thus, although we believe our mean age to be statistically valid, we would have expected our multiple primary patients to have had a younger average age, and we cannot explain this finding.

We also found a higher distribution of synchronous tumors on the right side of the colon (39.8 percent of synchronous *vs.* 31.7 percent of single; $P < 0.05$), and single tumors in the sigmoid colon (30.7 percent of synchronous *vs.* 42.3 percent of single; $P < 0.001$). Again, this finding was consistent with that of some previous reports[13, 16] but disagreed with findings of others.[18, 31, 32] More importantly, 64 percent of tumors

were in different segments of the colon, with 63 percent of these located in completely separate segments. The surgical implication of this pattern of tumor location is that a more extensive resection, including either modified hemicolectomy for tumors in adjacent segments or subtotal colectomy for tumors in separate segments, may be required in majority of patients with synchronous colon tumors. These findings also imply that there may be two different etiologies for synchronous tumors; an increase in local carcinogen exposure could explain multiple primaries that are clustered in the same segment of bowel. Conversely, finding tumors in different areas of the bowel implies a germline defect that could involve oncogene activation, loss of function of tumor suppressor genes, or both, affecting entire colon mucosa.[41] Until further genetic correlation is available, however, specific reasons some patients develop synchronous colon tumors will remain largely unknown.

Although majority of synchronous tumors in this study were of an early stage (Stages O, I), patients with synchronous tumors more often presented at more advanced stages (Stages II, III, IV) than patients with single colon cancers, when the highest stage lesion was considered (69 *vs.* 59 percent, respectively, $P < 0.05$). Again, some authors have found similar results,[12] whereas others have found no difference in distribution by stage.[20, 27]

Because of this previously mentioned variability in reported incidence and relatively rare occurrence of synchronous tumors, long-term prognosis of patients with such multiple colon primaries remains unsettled. Again, some studies have demonstrated a higher survival in patients with synchronous colon tumors,[23, 28, 29] although others have demonstrated a higher survival for patients with a single colon primary.[24, 31] In this study, there was no difference in five-year survival between patients with synchronous and single colon primaries when highest stage synchronous lesion was considered, a finding that has also been reported previously.[26, 27, 30, 32, 34]

There are several differences between our study and prior studies. First, most other studies have too few patients with synchronous colon tumors to accurately predict long-term survival. It is of note that our study is the largest Western series of synchronous colon cancers to date; only the report of Kaibara *et al.*[30] from Japan (763 patients) is larger. However, these authors reported only cummulative survival and made no comparison with patients with single colon tumors. Second, there has also been variability in staging criteria used, with only some studies reporting stage-specific survival and most using modified Dukes classification.[42] For example, Adloff *et al.*[32] reported no difference in five-year survival between 55 patients with synchronous colon tumors and 982 patients with single colon tumors based on Dukes stage. However, as with other studies, there were too few patients in synchronous cancer group for survival calculation by stage to be statistically valid. Unlike previous studies, we report five-year survivals calculated by life table methods and based on currently accepted TNM classification. Large size of our series and significant differences in survival between each stage for synchronous cases add statistical power to our finding of no difference between disease-specific survival of patients with synchronous and those with solitary colon primaries.

SUMMARY

We identified 4,878 patients with colon cancer from an 18-year database, of which there were 160 patients with 339 synchronous colon primaries, for an incidence of 3.3 percent. Synchronous tumors most commonly presented as two tumors (94 percent of cases) in different segmental regions of the colon (64 percent of cases). Synchronous tumors were most frequently located on right side of colon, whereas solitary tumors were more frequently on left side. Disease-specific five-year survival for patients with synchronous colon primaries determined by highest stage lesion was the same as survival of patients with solitary cancers, on a stage-for-stage basis.

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