Title
Adenoma recurrences after resection of colorectal carcinoma: results from the Southwest Oncology Group 9041 calcium chemoprevention pilot study.

Journal
Annals of surgical oncology, 10(8)

ISSN
1068-9265

Authors
Chu, David Z J
Chansky, Kari
Alberts, David S
et al.

Publication Date
2003-10-01

Peer reviewed

Annals of Surgical Oncology, **10**(8):870–875
DOI: 10.1245/ASO.2003.03.037

Adenoma Recurrences After Resection of Colorectal Carcinoma: Results From the Southwest Oncology Group 9041 Calcium Chemoprevention Pilot Study

David Z. J. Chu, MD, Kari Chansky, MS, David S. Alberts, MD, Frank L. Meyskens, Jr., MD, Cecilia M. Fenoglio-Preiser, MD, Saul E. Rivkin, MD, Glenn M. Mills, MD, Jeffrey K. Giguere, MD, Gary E. Goodman, MD, James L. Abbruzzese, MD, and Scott M. Lippman, MD

Background: Colorectal adenomas are the usual precursors to carcinoma in sporadic and hereditary colorectal cancers (CRC).

Methods: A total of 220 CRC patients (stages 0, I, and II) were randomized prospectively in a double-blind pilot study of calcium chemoprevention by using recurrent colorectal adenomas as a surrogate end point. This trial is still in progress, and we report the preliminary findings on adenoma recurrence rates.

Results: Synchronous adenomas were present in 60% of patients, and cancer confined in a polyp was present in 23% of patients. The overall cumulative adenoma recurrence rate was 31% (19% in the first year, 29% for 2 years, and 35% for 3 years). The recurrence rates were greater for patients with synchronous adenomas: 38% at 3 years ($P = .01$). Lower stage was associated with higher adenoma recurrence rates ($P = .04$). Factors including age, sex, site of primary cancer, and whether the cancer was confined to a polyp were not significantly associated with differences in adenoma recurrence rates.

Conclusions: The substantial adenoma recurrence rate in patients resected of CRC justifies colonoscopic surveillance on a periodic basis. Patients with higher rates of adenoma recurrences, such as CRC with synchronous adenomas, are ideal subjects for chemoprevention trials.

Key Words: Adenoma—Colorectal cancer—Synchronous adenoma—Adenoma recurrence rate.

Adenomas are precursor lesions to colorectal carcinoma (CRC).[1,2] The stepwise progression described as the polyp-cancer sequence is characterized by well-recognized morphological and histological changes. For example, a small tubular adenoma acquires villoglandular features as it grows in size. On the molecular level, the polyp or adenoma-cancer sequence reflects a progressive accumulation of genomic defects.[3,4] In general, a single adenoma presents a risk for developing into cancer with a rate of approximately .25% to 1% per year, and this relationship holds for sporadic CRC.[5–8] This transformation rate is probably even higher for inherited CRC.[9]

The incidence of CRC in the United States has been approximately 43 per 100,000 population, and it ranks as the second most common cause of cancer deaths in men and women: 57,000 individuals yearly. There has been a slight decline in the incidence and mortality in the past two decades, with stabilization of the incidence rates since the mid 1990s.[10] Combined strategies aimed at reducing the incidence of adenomas by endoscopic

Received March 15, 2002; accepted June 20, 2003.

From the City of Hope National Medical Center (DZJC), Duarte, California; Southwest Oncology Group Statistical Center (KC), Seattle, Washington; University of Arizona Cancer Center (DSA), Tucson, Arizona; University of California (FLM), Irvine, Orange, California; University of Cincinnati Medical Center (CMF-P), Cincinnati, Ohio; Puget Sound Oncology Consortium (SER, GEG), Seattle, Washington; Louisiana State University (GMM), Shreveport, Louisiana; Greenville Community Clinical Oncology Program (JKG), Greenville, South Carolina; and M. D. Anderson Cancer Center (JLA, SML), Houston, Texas.

Address correspondence and reprint requests to: Southwest Oncology Group (SWOG-9041) Operations Office, 14980 Omicron Drive, San Antonio, TX 78245-3217.

polypectomy have succeeded in decreasing the rates of CRC.[11–13] Several recent and current CRC chemoprevention trials have used or are using the rate of recurrent adenomas as the primary end point. The reduction in the rates of recurrent adenomas or the reduction of the adenoma growth rates can hypothetically lead to lower rates of CRC.

In individuals already diagnosed with CRC, the adenoma is significant in several ways. Adenomas found in association with CRC predict a higher rate of synchronous and second metachronous CRC.[14,15] The rate of adenoma recurrence in patients with CRC resected for cure has been reported with a wide range of 8% to 46%[14–18] by follow-up endoscopy. This wide variance can be explained by the different intervals and compliance rates of postoperative endoscopy, the retrospective nature of the studies, and variations in patient characteristics. Determining accurate rates of adenoma recurrence in a particular population will allow improved recommendations for surveillance and better selection of individuals who may benefit from chemoprevention.

The Southwest Oncology Group study S9041 is a multicenter pilot and feasibility trial involving double-blind administration of oral calcium carbonate or placebo in patients with completely resected CRC. After a 3-month run-in period, compliant patients were randomized to either calcium carbonate (Caltrate) 1800 mg/day or placebo daily for 5 years. The primary end points were feasibility of accrual and follow-up and protocol compliance, but an important secondary end point was adenoma recurrence. To date, there are 75 patients still on protocol treatment, and the final results, including a comparison by study arm, will be reported on completion. This article reports on a preliminary review of the adenoma recurrence data. This is the second study to report the recurrence rate of adenomas found in patients with resected CRC from a prospective randomized multi-institutional trial. Previous reports have been either retrospective reviews or prospectively designed protocols with retrospective data acquisition, and most were from single institutions. In this study, we also examine the features associated with adenoma recurrence.

METHODS

Sixty two Southwest Oncology Group institutions enrolled 280 patients with resected CRC to the 3-month run-in phase of this study. Patients with stages 0, I, and II CRC (T4 excluded), including carcinoma confined within a polyp, were eligible. Patients with familial polyposis and inflammatory bowel disease were ineligible. Complete resection of CRC needed to be within 550 days before registration. The study subjects were randomized to calcium carbonate 1800 mg and placebo, given daily over 5 years after a 3-month placebo run-in period. Pre-enrollment colonoscopy was to be followed by repeat colonoscopies at 1, 3, and 5 years. Pathologic review was performed to confirm stage and histology of the CRC, synchronous adenoma (SA), and recurrent adenomas. Colonoscopy data collected prospectively included the site of primary CRC, synchronous and recurrent adenoma characteristics (number, size, histology, and site), and follow-up information, including tumor recurrence and sites, drug toxicity, and drug intake compliance. Sixty of the 280 initially registered patients did not continue to randomization, mostly because of refusal or failure to comply with study drug doses and schedules. Sixteen of the 220 patients who proceeded to randomization are currently ineligible because of inadequate run-in compliance ($n = 2$), failure to perform required baseline evaluations ($n = 4$), and insufficient documentation of eligibility criteria ($n = 10$). We report here on 192 eligible patients from both arms combined for whom we currently have follow-up data on the incidence and characteristics of recurrent adenomas, recurrence of tumor, and development of second CRC.

Because compliance with the follow-up colonoscopy schedule was variable (see Results), which poses many challenges for analysis, we report very basic recurrence rate information. The overall recurrence rate was calculated as the percentage of all patients ($n = 192$) who had at least one adenoma recurrence detected at any time during follow-up. The 1-year recurrence rate was calculated as the percentage of patients who had at least one adenoma recurrence reported within the first 12 months on the study among all patients who were at least 1 year out from randomization ($n = 188$). Similarly, the 2- and 3-year rates were calculated as the percentage of patients who had at least one adenoma recurrence reported within the first 2 and 3 years on the study, respectively, among all patients who were 2 and 3 years out from randomization at the time of analysis ($n = 141$ and $n = 92$, respectively). Although this method may underestimate the true recurrence rates, it was chosen to avoid the potential inflation of recurrence rates resulting from the exclusion of patients who had not undergone a recent colonoscopy.

Comparisons of rates by the various baseline factors were performed with a χ^2 test of association. These baseline factors were also considered together by using a logistic regression model with forward stepwise selection. For this part of the analysis, stage was considered

both categorically and as an ordered variable. The number of SAs at baseline was considered as an ordered variable, with increments as follows: 0 vs. 1 to 3 vs. ≥4 adenomas. Although the use of failure time analysis (e.g., the Kaplan-Meier method) was considered, it was deemed inappropriate because of the inability to determine when a recurrent polyp actually appeared.

RESULTS

The median age at randomization was 68 years (range, 31–90 years), and 62% were men. The site of CRC at baseline was rectal in 20% and colon in 80%. SAs were present in 60%, and 14% had more than four SAs. Tumor stage at baseline was stage 0 (carcinoma-in-situ) in 5%, stage I in 52%, and stage II in 43%. Cancer confined to a polyp was present in 24% of patients. Patients with more advanced CRC were not eligible.

Although the pre-enrollment colonoscopy was to be followed by repeat colonoscopies at 1, 3, and 5 years, a proportion of patients underwent their first follow-up colonoscopy at year 2 or later. A total of 79% of patients had undergone the requested 1-year colonoscopy by 15 months. However, eight of these patients had undergone the first colonoscopy (with negative findings) within 6 months of registration without a repeat at 1 year. Among patients who were at least 2 years out from randomization, 84% had undergone at least one follow-up colonoscopy by year 2. By 39 months, 52% of those patients who were 39 months out from randomization (n = 92) had undergone two follow-up colonoscopies, and 90% had undergone at least one.

The locations of recurrent adenomas are listed in Table 1. The 1-, 2-, and 3-year cumulative adenoma recurrence rates, calculated as described previously and broken down by year of detection, are listed in Table 2. Most recurrent adenomas were found in the first 2 years of follow-up. The overall recurrence rate for patients with any amount of follow-up (n = 192) was 31%.

As shown in Table 3, there was a statistically significant association between adenoma recurrence and the presence of SA at baseline, as well as the number of SAs at baseline ($P = .01$). The highest rate of recurrence (59%) was seen in patients with four or more SAs. In a logistic regression analysis, SA and stage were selected for inclusion via stepwise selection in a multivariate model ($P = .0003$ and .03, respectively). All other baseline factors were rejected. In this model, each incremental increase in the number of SAs at baseline (0 vs. 1–3 vs. ≥4) conferred an odds ratio of 2.43 (Table 4). The odds ratio for each one-step increase in stage was 1.84, but this relationship was evident only when SA was included in the model. When stage is considered alone (without adjusting for SA) as a categorical variable ($P = .09$) or as an ordered variable ($P = .13$) for adenoma recurrence, it does not reach statistical significance, a fact that is readily apparent by viewing the results in Table 3. There may be a weak relationship between baseline stage and SA (see Table 5) that could account for this effect.

TABLE 1. *Locations of first adenoma recurrences*

Variable	n (%)
Cecum	9 (17)
Ascending colon	11 (21)
Transverse colon	10 (19)
Left and sigmoid	5 (10)
Rectum	13 (25)
Both rectum and proximal colon	4 (8)

Location not reported in 8 patients.

TABLE 2. *The 1-, 2-, and 3-year adenoma recurrence rates and, for each rate, the breakdown of when recurrences were detected over the 1-, 2-, and 3-year intervals*

Follow-up time	Recurrence rate	No. First recurrences during each year			
		Year 1	Year 2	Year 3	Total
Overall (n = 192)	31%	36	16	8	60
1 y (n = 188)	19%	36			36
2 y (n = 141)	29%	28	13		41
3 y (n = 92)	35%	19	10	3	32

There were no statistically significant differences in adenoma recurrence rates when analyzed by age, sex, site of cancer, or whether the primary tumor was confined to a polyp. Among the 60 patients who had an adenoma recurrence, most (57%) had >1 recurrent polyp present, and 12% had >4 new polyps. Eleven patients (9%) had recurrent adenomas found on more than one occasion. These were separate recurrences, because each time the adenomas were excised endoscopically.

Eleven patients had had cancer recurrences at the time of this review. Eight of these 11 patients had stage II CRC at baseline (10% recurrence rate for stage II). Three had stage I cancer (3% recurrence rate for stage I). All three recurrences in patients with initial stage I disease were local and regional, whereas four of the eight recurrences in stage II disease were distant. Four second primary CRCs were found, three of which were in patients with SAs. There were 29 deaths among the study patients, 7 of whom were among the 11 who had recurrent disease.

DISCUSSION

Current efforts in prevention of CRC highlight the important role of colorectal adenomas. Surveillance and

TABLE 3. *Overall adenoma recurrence rates for various baseline factors*

Baseline characteristic	Category (n)	Rate
Site of primary tumor	Colon (154)	32%
	Rectum (38)	29%
	Confined to polyp (46)	24%
	Not confined to polyp (146)	34%
Stage	0 (11)	37%
	I (99)	24%
	II (82)	39%
Age	60 y (51)	24%
	60–70 y (59)	32%
	70 y (82)	36%
Sex	Female (72)	28%
	Male (120)	33%
Synchronous adenomas (SA) at baseline	SA present (116)	38%
	SA absent (76)	21% ($P = .01$)
	$\geq$ 4 SAs (27)	59%
	0–3 SAs (165)	27% ($P = .0007$)

endoscopic excision of polyps reduces the incidence of CRC.[11–13] Chemoprevention with calcium in sporadic adenomas[19] and nonsteroidal anti-inflammatory drugs in familial polyposis[20] and sporadic adenomas,[21] for example, has reduced the number and frequency of recurrent adenomas. These studies have also extended our knowledge of the nature of adenoma recurrence. The ultimate goal is linking the clinical behavior of adenomas and subsequent presentation of CRC.

In the setting of sporadic adenomas, the recurrence of adenomas has been found to be affected by several variables: number, size,[22] and histology,[23] as well as location of index adenomas, age, and sex.[24] Several authors have clustered the characteristics of size ($>$1 cm) and histology (villous or dysplastic component) to define advanced adenomas. A left to right shift on the intraluminal location of the recurrent adenomas has been reported,[22,25] and the more proximal colonic presentation of recurrent adenomas has implications for methods of surveillance: colonoscopic as opposed to flexible sigmoidoscopy.

In the setting of resected CRC, surveillance for recurrent adenomas and second primary CRC has been based on retrospective studies and a few prospective studies. The incidence of adenomas found in the postoperative surveillance has a wide range of 8% to 46% during an average follow-up period of 3 years.[14–18] Neugut et al.[15] reported retrospectively on 290 patients after eliminating 61 patients from the initial review because of lack of complete data or $<$1 year of follow-up, and they found the adenoma recurrence rate to be 30%. In this study, the cumulative 3-year incidence is 31% (n = 192), and for patients who were followed up for at least 3 years, a conservative estimate of the incidence rate is 35% (n = 92). Considering the rate of missed adenoma of any single colonoscopic procedure, the rate of recurrent adenomas is more reproducible when reported as a cumulative rate after two or three surveillance procedures. The only baseline characteristic found in this study to be significantly associated with the rate of recurrent adenoma was the presence of SA. In the presence of SA, the overall rate is 38%, compared with 21% without SA ($P = .01$). The number of SAs was also important. Four or more SAs was found to have a recurrent adenoma rate of 59%, which is significantly greater than the rate of fewer than three SAs (27%; $P = .0007$). Location, age, and sex did not significantly change the rate of recurrent adenomas. Age showed a positive trend for age $>$70 years but did not reach statistical significance. The association of stage of CRC with recurrent adenomas was weak and linked to the presence of SA (Tables 4 and 5).

TABLE 4. *Multivariate logistic regression model for significant factors for recurrent adenomas*[a]

Factor	OR	*P* value
SA (0 vs. 1–3 vs. 4)	2.43 (1.50–3.94)	.0003
Stage (0 vs. I vs. II)	1.84 (1.05–3.24)	.034

[a] Factors considered but rejected from model via forward stepwise selection were age, sex, site of primary cancer, and cancer confined to polyp.

SA, synchronous adenoma; OR, odds ratio.

TABLE 5. *Distribution of synchronous adenomas by stage*

	Number of synchronous adenomas at baseline		
Stage	0	1–3	$\geq$4
0	2 (18%)	6 (55%)	3 (27%)
1	35 (35%)	49 (49%)	15 (15%)
2	38 (46%)	35 (43%)	9 (11%)

This finding will have to be investigated and confirmed in future studies.

CRCs confined to a polyp are usually small tumors presenting in a villoglandular polyp and could be classified as a small CRC within SA. The fact that polypoid carcinomas, or carcinomas confined to a polyp, were not associated with increased rates of adenoma recurrence (Table 3) indicates, surprisingly, that their behavior is rather more like a solitary CRC and is not associated with characteristics of SA.

Slater et al.[26] found that CRCs on the right side of the colon were more likely to be associated with SA. Some of these patients probably had the hereditary nonpolyposis colon cancer syndrome, which today would have been recognized by the younger age and the family history of gastrointestinal and uterine cancers and confirmed by microsatellite instability and genetic testing. A survey of the literature failed to reveal any other prognostic factors for recurrent adenomas other than SAs in this patient population of resected colorectal cancer.[14–18,27] It is possible that the significant adenoma factors found in the context of sporadic adenoma could also be found to affect adenoma recurrences in resected CRC patients. For example, a larger prospective study will be required to investigate size, histology, right- or left-sided location of SA, or other characteristics of the presenting CRC, such as location, tumor differentiation, and stage, in relationship to adenoma recurrence rates and to the rates of second primary CRC development. Furthermore, the interpretation and significance of these clinical and pathologic characteristics of recurrent adenomas in the context of the adenoma-carcinoma sequence need to also be linked to molecular markers associated with the underlying genetic changes. The implication is that in chemoprevention studies, meaningful biomarkers need to be identified and linked with known significant clinical factors in generation of new adenomas and carcinomas in the large gut.

The incidence of SA in this series of 60% is higher than the 30% to 36% observed in most series.[14,28,29] It is clear that the rate of SA will have to be figured into the results of adenoma recurrence in any future studies.

The rate of second primary CRC in patients treated for CRC ranges from .2% to 1% per year of follow-up.[14,15,30,31] This rate increases by 2-fold for CRC with SA.[14,30] It will be important if this rate of development of second CRC is also increased by the presence of recurrent or metachronous adenomas. The rate of second CRC is also significantly increased in young patients (<50 years old and, especially, <40 years old).[32] Our study had only 15 (7.8%) patients younger than 50 years old and 3 (1.5%) patients <40 years old and therefore could not adequately address the issue of younger age and second adenomas in CRC patients. Clearly, many of the factors linked with recurrent adenomas will also have to be analyzed, in future studies, with respect to the end point of second primary CRC.

The intergroup adjuvant chemotherapy trial (0089) reported a 1.5% rate of second primary CRC in 5 years among 3278 patients.[33] This rate is seven times higher for CRC than that for individuals entered in the National Polyp Study.[13] This study, the largest to date, confirms that the patient population with resected CRC is among the highest-risk groups for developing a second sporadic CRC. Future chemoprevention studies should target individuals with resected CRC, use recurrent adenomas as a major end point, and consider the presence of SA as an added risk factor. Prevention studies thus far have used adenomas as the end point, which ultimately is secondary in importance to cancer development. To demonstrate CRC prevention, future studies must be performed in high-risk groups, such as individuals with resected CRC or groups with sporadic adenomas and inherited polyposis.

ACKNOWLEDGMENTS

The acknowledgments are available online at www.annalssurgicaloncology.org.

REFERENCES

1. Jackman RJ, Mayo CW. The adenoma-carcinoma sequence in cancer of the colon. *Surg Gynecol Obstet* 1951;93:327–30.
2. Morson BC. The polyp-cancer sequence in the large bowel. *Proc R Soc Med* 1974;67:451–7.
3. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990;61:759–67.
4. Boland CR, Sato J, Saito K, et al. Genetic instability and chromosomal aberrations in colorectal cancer: a review of the current models. *Cancer Detect Prev* 1998;22:377–82.
5. Eide TJ. Risk of colorectal cancer in adenoma-bearing individuals within a defined population. *Int J Cancer* 1986;38:173–6.
6. Otchy DP, Ransohoff DF, Wolff BF, et al. Metachronous colon cancer in persons who have had a large adenomatous polyp. *Am J Gastroenterol* 1996;91:448–54.
7. Morson BC, Bussey HJR. Magnitude of risk for cancer in patients with colorectal adenomas. *Br J Surg* 1985;72(Suppl):S23–8.
8. Wilson LS, Lightwood J. Model of estimated rates of colorectal cancer from polyp growth by year of surveillance. *J Med Screen* 2001;8:187–96.
9. Rijcken FEM, Hollema H, Kleibeuker JH. Proximal adenomas in hereditary non-polyposis colorectal cancer are prone to rapid malignant transformation. *Gut* 2002;50:382–6.
10. Jemal A, Thomas A, Murray T, Thun M. Cancer statistics, 2002. CA Cancer J Clin 2002;52:23–47.
11. Thiis-Eversen E, Hoff GS, Sauar J, Langmark F, Majak BM, Batn MH. Population-based surveillance by colonoscopy: effect on the incidence of colorectal cancer. Telemark Polyp Study I. *Scand J Gastroenterol* 1999;34:414–20.
12. Atkin WS, Morson BC, Cuzick J. Long-term risk of colorectal

cancer after excision of rectosigmoid adenomas. *N Engl J Med* 1992;326:658–62.
13. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Work group. *N Engl J Med* 1993;329:1977–81.
14. Chu DZJ, Giacco G, Martin RC, Guinee VF. The significance of synchronous carcinoma and polyps in the colon and rectum. *Cancer* 1986;57:445–50.
15. Neugut AI, Lautenbach E, Abi-Rached B, Forde KA. Incidence of adenomas after curative resection for colorectal cancer. *Am J Gastroenterol* 1996;91:2096–8.
16. Khoury DA, Opelka FG, Beck DE, Hicks TC, Timmcke AE, Gathright JB. Colon surveillance after colorectal cancer surgery. *Dis Colon Rectum* 1996;39:252–6.
17. Patchett SE, Mulcahy HE, O'Donoghue DP. Colonoscopic surveillance after curative resection for colorectal cancer. *Br J Surg* 1993;80:1330–2.
18. Barlow AP, Thompson MH. Colonoscopic follow-up after resection for colorectal cancer: a selective policy. *Br J Surg* 1993;80: 781–4.
19. Baron JA, Beach M, Mandel JS, et al. Calcium supplements for the prevention of colorectal adenomas. *N Engl J Med* 1999;340:101–7.
20. Steinbach G, Lynch PM, Phillips RKS, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med* 2000;342:1946–52.
21. Baron JA, Cole BF, Mott LA. Aspirin chemoprevention of colorectal adenomas. *Proc Am Assoc Cancer Res* 2002;43:669.
22. Martinez ME, Sampliner R, Marshall JR, Bhattacharyya AK, Reid ME, Alberts DS. Adenoma characteristics as risk factors for recurrence of advanced adenomas. *Gastroenterology* 2001;120:1077–83.
23. Yang G, Zheng W, Sun QR, et al. Pathologic features of initial adenomas as predictors for metachronous adenomas of the rectum. *J Natl Cancer Inst* 1998;90:1661–5.
24. Jensen P, Krosgsgaard MR, Christiansen J. Prognostic model for patients treated for colorectal adenomas with regard to development of recurrent adenomas and carcinoma. *Eur J Surg* 1996;162: 229–34.
25. Nusko G, Mansmann U, Wiest G, Brueckl W, Kirchner T, Hahn EG. Right-sided shift found in metachronous colorectal adenomas. *Endoscopy* 2001;33:574–9.
26. Slater G, Fleshner P, Aufses AH. Colorectal cancer location and synchronous adenomas. *Am J Gastroenterol* 1988;83:832–6.
27. Cuquerella J, Orti E, Canelles P, et al. Colonoscopic follow-up of patients undergoing curative resection of colorectal cancer (in Spanish). *Gastroenterol Hepatol* 2001;24:415–20.
28. Langevin JM, Nivatvongs S. The true incidence of synchronous cancer of the large bowel. A prospective study. *Am J Surg* 1984; 147:330–3.
29. Scorza R, De Monti M, Ghilardi G, Sgroi G, Kunkl E. Endoscopy and surgery. A combined strategy for diagnosis and therapy of polyposis-cancer sequence in the colon. *Panminerva Med* 2001; 43:21–6.
30. Jensen P, Krogsgaard MR, Christiansen J. Prognostic model for patients treated for colorectal adenomas with regard to development of recurrent adenomas and carcinoma. *Eur J Surg* 1996;162: 229–34.
31. Togashi K, Knonishi F, Ozawa A, et al. Predictive factors for detecting colorectal carcinomas in surveillance colonoscopy after colorectal cancer surgery. *Dis colon Rectum* 2000;43(Suppl):S47–53.
32. Shureiqi I, Cooksley CD, Morris J, Soliman AS, Levin B, Lippman SM. Effect of age on risk of second primary colorectal cancer. *J Natl Cancer Inst* 2001;93:1264–6.
33. Green RJ, Metlay JP, Propert K, et al. Surveillance for second primary colorectal cancer after adjuvant chemotherapy: an analysis of intergroup 0089. *Ann Intern Med* 2002;136:261–9.