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

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**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.
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polypectomy have succeeded in decreasing the rates of CRC. Several recent and current CRC chemoprevention trials have used or are using the rate of recurrent adenomas as the primary endpoint. 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. The rate of adenoma recurrence in patients with CRC resected for cure has been reported with a wide range of 8% to 46% 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 $\chi^2$ 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