FU adjuvant arm of this particular protocol, but the difference between the adjuvant and control groups is not statistically significant at this time (See addendum).

The remaining concern regarding this trial of adjuvant 5 FU for colorectal cancer is the possibility of "burying" an advantage from this approach in the subgroup of the whole by focusing on a comparative analysis of the total colorectal group with and without the adjuvant. The rectal and colon lesions were actually randomized separately to allow homogeneity and this fact will be used at a later date to conduct separate analyses by site when the numbers of patients involved are larger, and the followup period longer. Although the rectal lesions in the ongoing multihospital study in New York have somewhat better results in the adjuvant 5 FU group (as opposed to no difference with colon lesions) this difference is far from statistical significance.[4] It is of interest that the small groups of rectal cancers in our study have grossly identical survival curves thus far despite a more prolonged course of adjuvant 5 FU therapy than used in the New York Study.

The initial studies of Rousselot and coworkers[7] using historical controls seemed to indicate benefit from adjuvant 5 FU with colorectal lesions in patients in a higher risk category (Dukes' C). However, the current prospective clinical trial from this same group fails to even suggest this difference and our data are in agreement with this latter finding. One might conclude from all of these incomplete data that any real differnce between adjuvant and control groups in a subcategory of the whole must be relatively small, or it would have been more apparent in the data that have been presented.

Conclusions

From our findings to date, we do not believe that the benefit of prolonged adjuvant therapy with 5 FU for patients undergoing "curative" surgery for colorectal cancer is adequate to justify its' general use. In time, minor degrees of benefit from this approach might become evident for all patients, or for patients in selected subgroups, but further evaluation to substantiate this must be accomplished before this approach can be recommended. Future trials of adjuvant chemotherapy for colorectal cancer may be more justified with a combination of chemotherapeutic agents or hopeful new agents, or immuno-adjuvants that are found to be effective for recurrent large bowel cancer.

Addendum

Since submission of this manuscript the results showing benefit from adjuvant 5 FU in the COG study have become statistically significant (Grage, T. E.; personal communication). It is of interest that the COG study differs from ours both in route of drug administration (intravenous) and scheduling of maintenance 5 FU (single weekly dose).

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Discussion

(Note: Some of the discussants' remarks relate to both this paper and the following one by Dr. George Higgins. Such discussions follow both articles in this volume.)

Dr. Murray M. Copeland (Houston, Texas): The results of the study by Dr. Lawrence and his colleagues are in keeping with the results of other studies using 5-FU as an adjuvant to curative resection for colorectal cancer. The important difference between this study and a well-known study by the VA group which Dr. Higgins has been considerably involved in is that more intensive and longer duration of 5-FU was used in Dr. Lawrence's study. Nevertheless, on the basis of these studies it seems reasonable to conclude that 5-FU, given by itself, is probably not beneficial in prolonging the disease-free interval for patients who have had curative resections for colorectal cancer.

A study presently being conducted by Dr. Mavligit and Dr. Freireich at our institution is one in which BCG, therapy as an adjuvant to curative resection for colorectal cancer is being used. Although it is too early to draw significant conclusions or to compare this study with that of Dr. Lawrence, there is a suggestion that early recurrence is less frequent with the use of BCG therapy. Thus, it is exciting to consider the possibility that immunotherapy or combinations of immunotherapy and chemotherapy might have significant advantages as adjuvants to curative surgical resection of colorectal cancer.

The findings in the report by Dr. Higgins and his group are of interest, and strongly suggest that preoperative radiation is worthwhile in patients who have rectal and low sigmoid primary lesions. It is important to emphasize that Dr. Higgins' results, as reflected in the survival curves for patients who have had curative resections, may be more significant than indicated. This is because patients who had curative resections following radiotherapy could have a worse prognosis than patients who had curative resections in the control group. Thus the difference in the survival curves might be more significant, taking this into account.

The major concern is that the sites and extent of recurrences, I don't believe, are discussed, Dr. Higgins. Perhaps I'm wrong about that. I

read your paper over quickly. The incidence of recurrence would be of great interest. In particular, a deceased incidence of local recurrence could be the best indicator of the effectiveness of preoperative radiation therapy.

The advantage of preoperative versus postoperative radiation is controversial for these low-lying lesions. Studies are presently being conducted which in the future can be compared to this study to determine the relative value of preoperative versus postoperative radiotherapy.

Dr. LOREN J. HUMPHREY (Kansas City, Kansas): If one looks at the change in survivals of carcinoma patients over the last 50 years, there has been progress in the field in general. Improvement has come from three areas: early detection; more precise staging, as with Hodgkin's disease; and, as in the recent data with sarcomas, combined radical therapy.

The points I would like to address to these two papers are that the basic problem, it would appear, with the adjuvant chemotherapy may be the problem of dosage and immunosuppression. Dr. Lawrence and his group are very well aware of these problems, and I only rise to emphasize from a study Dr. Jewell and I have done, that while the survival data are too recent to give meaningful data, the data does favor the combined immunotherapy and chemotherapy group. Antibody studies of serum from these patients, however, do show that those patients having antibody before chemotherapy become antibody negative after; whereas with immunotherapy, an additional 50% had antibody. So it appears that we are going to have to find the proper dose of chemotherapy if it is to be adjuvant.

The reason I rise to make the point about staging is my concern with radiation therapy, although one must endorse and support this type of randomized study. However, if one were to accept the fact that the nodal incidence were the same in the VA study, one would have to entertain that the low dose of radiation therapy indeed eliminated cancer in the lymph nodes giving the difference in incidence of metastatic disease in lymph nodes.

The problem, then, is severe; we lose a very important aspect of cancer management: proper staging; we do not know the stage of a significant number of those patients. I believe in the future that we will need this staging to decide whether to go along with just surgery or whether to add postoperative radical radiation therapy or chemotherapy.

My question to Dr. Lawrence is: Are you going to use a much lower dose, or randomize treatment into two different doses?

Dr. J. SHELTON HORSLEY, III (Closing discussion): There are several points I would like to re-emphasize in Dr. Lawrence's presentation. One is the use of the world "preliminary." This in a way answers the question Dr. Humphrey asked: Are we going to change our dosage? Actually, this has been submitted to statistical analysis, and our statistician tells us that to increase the confidence in our results we should follow these patients for another three to four years, which we plan on doing, and hope we will have the privilege of presenting those data in the not-too-distant future.

Also, someone might ask: How about Dukes' C patients? Is there any difference? Certainly in Rousselot and Grossi's work the most striking differences were in Dukes' C patients. In our patients the Dukes' C showed no difference between those in the 5-Fluorocuracil and those in the control group.

We administered the drug orally postoperatively for patient convenience. We feel that this was a satisfactory way to administer the drug, as witnessed by the fact that we did get some toxicity. I don't think it was a homeopathic dose. It was well tolerated by the patient. It was taken orally in orange juice or water.

I appreciate Dr. Copeland's remarks. We have had no experience with BCG, but we follow his leadership in this national study, and we look to him for suggestions of other modes of therapy that perhaps will be more effective.

As Dr. Humphrey has pointed out, one of the problems in this type of study may be the proper dose. We are not sure what the proper dose is under these circumstances, and look for help from him and other groups regarding their immunologic studies that perhaps will pin down what is and what isn't a proper dose.