Diagnosis and Management of Recurrent Colorectal Cancer

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Justification for the management of recurrent colorectal cancer begins with proof that the ultimate outcome measured by survival can be influenced. To do this, we must prove there is value to follow-up of colorectal cancer patients. Without follow-up, the management of recurrent cancer is limited.

Key words: colorectal cancer, survival, resection

INTRODUCTION

In 2008, it is estimated that there will be over 154,000 new cases of colorectal cancer in the United States. Over 90% of these will have curative resections. The overall recurrence of colorectal cancer has been reported at between 8 and 50%. Patients with recurrence are the ones who would potentially benefit from a surveillance program. Survival enhancement is therefore possible for between 12,000 and 76,000 patients.

Patients with stage IV disease with residual cancer following resection would not be candidates. Similarly, patients with stage I disease are at such a low risk for recurrence that follow-up would seem imprudent. The greatest risk of recurrence occurs with stage II and III disease. Additional modifiers of recurrence risk have included race, presentation, grade and multiple biological molecular markers including flow cytometric characteristics, P53 status, DCCG, P27 and P53. It would be nice to have a matrix of these factors, which would accurately predict recurrence, but so far that has not been developed.

A rational follow-up program will recognize that there are specific patterns of recurrence. The wound is involved with recurrence about 1% of the time. The most common site of recurrence has been identified as the liver. For rectal cancer, the risk of regional recurrence ranges from 5 to 40%. Increasingly, the role of adequate surgical technique has been emphasized so that recurrence rates in the pelvis of less than 10% are to be expected as the second most common site of recurrence. The brain and bone marrow are a distant third site of recurrence.

To identify a recurrent disease, multiple tests are available. There have been several studies that have tried to identify which tests are most valuable to order at what time interval. The work of Polk and Spratt has noted that follow-up every 2 to 4 months is appropriate if you would like to identify 2% to 3% of patients with recurrence at each interval. They recommend this follow-up for 2 years and then follow patients at 6-month intervals for an additional three years. Over 90% of recurrences will be identified in this 5-year period.

The indiscriminate use of tests to identify recurrence is costly. Therefore, a knowledgeable physician will employ those tests that have the highest yield at the most reasonable cost. By understanding the patterns of recurrences as well as the predicted value of each test, the appropriate panel of tests can be identified. The most sensitive test to determine the presence of recurrence is to listen to the patient. The history and physical examination will suggest recurrent disease at the earliest point of time detectable by any tests. The symptoms related to disease recurrence that are nonspecific include vague abdominal pain, weight loss, malaise, cough, abdominal pain, and change in bowel habits. These symptoms frequently occur in postoperative patients and one must be prudent in assessing patients with these symptoms. That is not to say that every patient with a cough, headache, or a new symptom has recurrent cancer. On the other hand, patients who say that they feel well and are not having any symptoms, then there is good reason to believe that the patient is likely doing well.

There are multiple biochemical tests that can be ordered. These include liver function tests, CBC, carcinoembryonic antigen (CEA), CA19-9 and CA125. Only CEA has proven to be of significant help in identifying early recurrence. CEA will identify 65% of patients at the earliest point of detectable disease by any test. The combination of history, physical and CEA will identify essentially all
patients with recurrent disease at the earliest point of detectable disease.13-19

Rarely is recurrent colorectal cancer detected through a CBC count. Anemia can be associated with many other causes and rarely helps identify recurrent colorectal cancer. Although anastomotic recurrences can occur, they are present in less than 5% of patients with colon cancer and most patients are not likely to be losing blood due to recurrent disease.20 Alkaline phosphatase has long been regarded as the most sensitive of liver function tests to identify hepatic metastases. This test, however, is rarely an early sign of liver disease and it is not as sensitive as carcinoembryonic antigen. Similarly, bilirubin and transaminases are only late signs and not helpful in the identification of early recurrences.

Physical examination is less useful. About 30% of patients will have physical signs present at the earliest point of detectable disease. Proctoscopic exams will identify about 20% of patients with recurrent pelvic disease. Most patients with recurrent pelvic disease, who have access to their pelvis through the rectum or vagina, will have palpable disease. Chest x-ray will similarly identify about 20% of patients with recurrent pulmonary disease.

CAT and liver scans are very sensitive and will identify about 90% of patients with recurrent liver disease; however, they are also very expensive.21 For this reason, in most practices they are relegated to confirmatory testing rather than a routine screening for cancer recurrence. A CAT scan is also very helpful for identifying recurrent pelvic disease. As pointed out earlier, however, most pelvic recurrences are palpable. CEA is less useful for identifying recurrent pelvic disease than for identifying recurrent hepatic or brain metastases. It is, therefore, generally less useful for rectal cancer than it is for colon cancer. Positron Emission Tomography (PET) scanning is the most sensitive test for recurrent disease, but it similarly is very expensive.22 It also has a false positive rate that decreases at specificity. Rectal cancer can probably best be followed by endoluminal ultrasound.23-26 Multiple studies have shown that ultrasound is extremely sensitive for identifying pelvic recurrences. It is less useful for evaluating colon cancers, even though there are ultrasound machines that can be placed through a colonoscope. Scarring, tissue distortion, and displacement of organs can decrease the specificity of endorectal ultrasound, but it is still very useful in noting changes in these abnormalities at a very early point in the evolution of recurrent pelvic disease.

Once a recurrent disease is suspected either through change in symptoms, or elevated carcinoembryonic antigen, or physical finding, then confirmatory testing is necessary. Typically, a CAT scan would be the first test. A CAT scan of the chest, abdomen and pelvis is most likely to identify recurrent disease. CAT scan directed biopsies are often then possible to help confirm that the abnormality is truly cancer and not some postoperative change or other benign nodule. Endoscopy should also be performed to rule out intraluminal recurrence or metastatic disease.21, 27, 28 If these tests are unrewarding, then a PET scan is the next test to identify recurrence. It has a high sensitivity but a lower specificity in identifying recurrence.

Monoclonal antibodies have also been recommended; however, because these are mouse antibodies, patients who have these tests are at risk for not being able to repeat the test secondary to allergic reaction. Therefore, we find this to be the third line of testing and rarely necessary.26

STUDIES EVALUATING THE VALUE OF THE EFFECTIVENESS OF FOLLOW-UP

By pooling the data from various randomized and comparative cohort studies, we recently demonstrated a statistically significant difference in cumulative 5-year survival for those patients undergoing intensive follow-up.29 Results of our meta-analysis showed that patients who were in the intensive follow-up group were two and one-half times more likely to have a curative re-resection than those patients in the control group. With respect to those patients undergoing intensive follow-up, they had a 3.62 times higher survival rate after recurrence than did the controls.

RECURRENT TREATMENT

It has been well documented in multiple studies that recurrences of the liver can be resected.30 It is clear that women do better than men,31 patients with fewer than 4 metastases do better than those with 4 or more metastases in the liver, and those that recur a short time after initial resection seem to do less well than those who are high grade or recur at a more distant interval after resection of the primary. Similarly, lung and brain metastases can be resected.32 Interestingly, all solid organ recurrence sights have about a 25 to 30% cure rate when resected.31, 33, 34, 35, 55, 64, 65 The issue, then, is whether follow-up can identify recurrent disease at an earlier point in time that will render these patients more likely to be cured.35

Locally recurrent rectal cancer presents a considerable therapeutic challenge. The incidence of recurrent rectal cancer after primary resection has been reported to vary from 3% up to 50%, even though the most recent standards demand that proper surgical technique (total mesorectal excision) achieve a less than 10% local recurrence rate without (neo-)adjuvant treatment.38 Sixty percent of the recurrences occur during the first 2 years after surgery. The natural course of locally advanced, unresectable rectal cancer results in a median survival time of only 7 to 8 months without any treatment.39, 40 during which severe disabling problems accumulate such as severe pain, bleeding, bowel and urinary obstruction, and fecal and urinary leakage.

Recent studies have demonstrated that recurrent disease remains confined to the pelvis in approximately 25-50% of the patients.41 This has been justification to suggest an aggressive surgical approach to achieve local tumor control, both for improvement and prevention of symptoms and for possible long-term cure.42, 43 With extended en-bloc resection, one third of the patients have a chance for cure,44 which may even further improve in combination
with adjuvant chemotherapy and external or intra-operative radiation therapy (IORT). 45

However, resection for recurrent rectal cancer has also been associated with a high morbidity and mortality. 46, 47 In addition, pelvic exenteration may interfere with the patient’s quality of life 48 as it may necessitate one or even 2 ostomies for urinary or fecal diversion.

As long as the pelvic floor is neither directly affected by the recurrent tumor or the extent of the surgical resection, restoration of bowel and urinary tract continuity and continence are technically feasible. Advanced techniques in the management of advanced pelvic tumors include ultralow sphincter-saving resection of the rectum with coloanal anastomosis on one hand, bladder-sparing or reconstruction of an orthotopic neobladder on the other hand. 49, 50

We analyzed our experience of managing locally recurrent rectal cancer with the aim of assessing the value and outcome of pelvic floor-sparing procedures and continence restoration. We report that they result in an improved quality of life without jeopardizing local cancer control and survival rates. Within the study period, 76 patients were explored for recurrent rectal cancer, of which 67 patients (male/female 45/22, age 32-81 years) had available follow-up data and were included in the analysis.

Preservation or restoration of intestinal and/or urinary continuity was achieved in 22 (33%) of the 67 patients. In 45 patients, neither urinary tract nor intestinal continuity could be restored, and the patient ended up with urinary tract and intestinal ostomies. Urinary continence was preserved or restored in 12 patients (7 and 5, respectively), intestinal continuity in 14 patients, which include 4 patients, in whom both urinary tract and intestinal continuity were restored. A temporary diverting ileostomy was necessary in 5 out 14 (36%) patients.

Despite the complexity of the surgical procedures, there was no perioperative mortality. Continence preservation did not result in an increased rate of complications as compared to the group without continence preservation. After a median follow-up time was 17 month (range 5-55 months), 11 out of 22 patients (50%) were still alive, of which 7 (31%) did not have any evidence of disease. Three patients died of non-cancer-related causes and were disease-free the time of death. When compared to the group without continence preservation, the “continence group” did not show any detectable negative impact on disease-free survival or overall survival (p=1 and p=0.55, respectively; see Figure 2). Thirty-two of the 45 patients (71%) without continence restoration were alive, of which 16 patients (35%) were disease-free.

Hahnloser et al, recently published their institutional experience with multimodality treatment for locally recurrent rectal cancer. 45 They reported a 5-year survival rate of 37% if the margins after surgical re-resection were negative, as opposed to an overall 5-year survival of 25%. In addition, they even demonstrated a benefit from surgical resection in many patients that were eventually not cured.

All patients in our study, who had successfully undergone a bowel continence preserving procedure, were highly satisfied with the functional and cosmetic results and the fact that a stoma could be avoided. Further studies will be necessary to correlate these subjective results with validated objective parameters.

**SUMMARY**

**DIJAGNOZA I TRETMAN RECIDIVANTNOG KOLOREKTALNOG KARCINOMA**


Ključne reči: kolorektalni karcinom, preživljavanje, lečenje

**REFERENCES**


