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Prognostic and predictive factors after surgical treatment for locally recurrent rectal cancer: A single institute experience☆

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Abstract

Objective: Resection of locally recurrent rectal cancer (LRRC) after curative resection represents a difficult problem and a surgical challenge. The aim of this study was to evaluate the results of resecting the local recurrence of rectal cancer and to analyze factors that might predict curative resection and those that affect survival.
Patients and methods: A retrospective review was performed in 50 patients who underwent surgical exploration with intent to cure LRRC between April 1998 and April 2005. All of the patients had previously undergone resection of primary rectal adenocarcinoma. Of these patients' charts, operation and pathology reports were reviewed. Primary tumor and treatment details, hospital of initial treatment and TNM stage were registered. The following data were collected concerning the detection of the local recurrence; date of recurrence, symptoms at the time of presentation and diagnostic work-up. Perioperative complication and date of discharge were also gathered. The recurrent tumors were classified as not fixed (F0), fixed at one site (F1) and fixed to two or more sites (F2) according to the preoperative and peroperative findings. Microscopic involvement of surgical margins and localization of recurrence were noted based on pathology reports.
Results: The median time interval between resection of primary tumor and surgery for locally recurrent disease was 24 (4–113) months. In a statistical analysis, initial surgery, complaints of patients, increasing number of sites of the recurrent tumor fixation in the pelvis, location of the recurrent tumor were associated with curative surgery. Curative, negative resection margins were obtained in 24 (48%) of patients; in these patients a median survival of 28 months was achieved, compared to 12 months ($p = 0.01$) in patients with either microscopic or gross residual disease. Primary operation and CEA level at recurrence were also found to be important factors associated with improved survival. There was no operative mortality and, the complication rate was 24%.
Conclusions: This study demonstrated that many patients with LRRC can be resected with negative margins. The type of primary surgery, symptoms, location, and fixity of recurrent tumor are associated with the increased possibility of carrying out curative resection. Previous surgery and curative surgery are significant predictors of both disease-specific survival and overall survival.

Keywords: Recurrent rectal cancer; Surgical treatment; Curative resection

Introduction

In patients who undergo radical surgery for rectal cancer, 4–30% develop locoregional relapse.[1–4] The survival of patients would be adversely affected by the presence of locoregional recurrence. Without treatment the median survival ranges from 3.5 to 13.0 months.[5,6] Isolated locoregional recurrence is the only site of disease in 25% of patients who die of recurrent rectal cancer.[7] Without treatment, these patients have a short life expectancy and tend to experience unpleasant symptoms, especially pain and their quality of life becomes extremely poor.[8] Radiotherapy, either alone or in combination with chemotherapy, allows symptomatic improvements in most patients but 5-year survival is usually less than 5%.[9,10] Nearly half of

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locally recurrent rectal cancers (LRRC) are located in the pelvis without distant metastasis and are technically amenable to surgical excision.[3,11] Treatment remains a difficult and challenging problem and no consensus exists as to an optimal treatment approach.

Complete surgical removal offers the only hope for long-term survival but can be associated with significant morbidity.[3,12] Improvement in outcome after resection of LRRC is based on achieving a complete R0 resection with microscopically negative margins. Unfortunately, even when carefully selected for surgery only 60% of patients with an apparent local-only recurrent rectal cancer are able to undergo an R0 resection.[13]

The aim of this study was to identify preoperative and intraoperative features of LRRC that predict the ability to achieve an R0 resection and to present the outcome of resection for LRRC in a single institution.

Patients and methods

Between April 1998 and April 2005, a total of 50 patients (33 males, 17 females) underwent surgical exploration for LRRC at the Department of Surgery of Istanbul University, Istanbul Medical Faculty. The median age of the 50 patients at the time of operation for local recurrence was 54 (range, 26–79) years. All of the patients had previously undergone resection of primary rectal adenocarcinoma. Of these patients' charts, operation and pathology reports were reviewed. Primary tumor and treatment details, hospital of initial treatment (Istanbul Medical Faculty or elsewhere) and initial TNM stage were registered.

The following data were collected concerning the detection of the local recurrence; date of recurrence, symptoms at the time of presentation and diagnostic work-up. Perioperative complication and date of discharge were also gathered. Microscopic involvement of surgical margins and localization of recurrence were noted based on pathology reports. Information concerning follow-up included the following: date of progression, site of progression, symptoms related to local recurrence, date of last follow-up or death and cause of death (tumor related or not) if applicable.

Preoperative evaluation

The aim of preoperative evaluation was to determine tumor resectability, to rule out metastatic disease outside the pelvis and to assess the general fitness of the patient and ability to withstand major excisional surgery. Each patient underwent computerized tomography of the thorax and abdomen to exclude distant metastases and to assess involvement of the bony pelvic ring. The presence of extensive abdominal or thoracic metastases was considered to be a contraindication to resection of the pelvic recurrence. Magnetic resonance imaging of the pelvis was performed to assess the location of the tumor, its direction of invasion, and involvement of local viscera and the pelvic sidewall structures. The number of sites of fixation to surrounding structures in the pelvis was determined preoperatively by cross-sectional imaging and again at the time of surgery. Contraindications to locally curative surgery as determined by imaging included extensive pelvic involvement, tumor encasement of the iliac vessels, and proximal sacral invasion above the level of the S2–S3 junction. Histologic confirmation of malignancy was obtained in most of the patients before surgical intervention.

Surgical procedures and adjuvant therapy

Surgical procedures were classified as follows: low anterior resection, abdominoperineal resection, total pelvic exenteration (removal of all pelvic viscera with the formation of a permanent colostomy and urinary diversion), or non-anatomic resection (resection not classified by any other mentioned before). All patients had received total irradiation of 45 Gy over five weeks with intravenous 5-fluorouracil during the first and fifth weeks (days 1–5 and 23–33) of radiotherapy during the treatment of primary tumor. Because of the irradiated for their initial treatment, radiotherapy was not given to any patients during treatment of LRRC. Adjuvant chemotherapy for the LRRC, usually 5-fluorouracil-based, was given to all patients.

Statistical analysis

Statistical analysis was performed with the statistical Package for social Sciences (SPSS) version 10.0 (SPSS Inc., Chicago, IL). The Chi-squared test was used to compare categoric variables. Cumulative survival curves were constructed with the Kaplan–Meier method and were calculated until the last follow-up visit or death. Comparison of factors that affect survival was made by log-rank test. A p-value less than 0.05 was considered statistically significant. Factors that were found to be significant in the univariate analysis were fed to a Cox regression analysis to test whether these factors were independent.

Results

Treatment of primary tumor

Between 1991 and 2005, 398 patients underwent curative surgery for a primary rectal cancer at Istanbul University, Istanbul Medical Faculty. In this period, 22 patients who had LRRC had evidence of extensive pelvic involvement or extrapelvic disease (according to the diagnostic work-up) and were considered unsuitable for surgery. Among the 50 patients who underwent resection for LRRC, 30 patients had surgery for the primary disease in our institution, 20 in elsewhere. The surgical procedure for primary tumor was anterior resection in 33 of the 50 patients, abdominoperineal excision of rectum (APR) in 17. All patients had received full dose radiotherapy as part of

Table 1
Patients and tumor characteristics ($n = 50$)

Characteristic	n
Median age in years (range)	54 (26–79)
Gender	
Male	33
Female	17
Referral source	
Own hospital	30
Elsewhere	20
Surgery for primary tumor	
Sphincter preserving surgery	33
Abdominoperineal resection	17
Primary T stage	
T2	7
T3	35
T4	8
Primary N stage	
N0	21
N1	19
N2	10
Localization of primary tumor	
Circumferential	31
Lateral	2
Anterior	12
Posterior	5
Symptoms	
Bleeding	21
Pain	26
Fistula	3
Localization of recurrent tumor	
Anastomosis	27
Pelvic	16
Posterior	4
Lateral	3
Types of surgery	
APR	19
Palliative surgery	14
Non-anatomic resection	13
Pelvic exenteration	3
Low anterior resection	1
Fixity	
F0	27
F1	7
F2	16
Median time to local recurrence (months)	24 (4–113)

the management of the primary rectal cancer. Patient demographics, treatment details and pathologic tumor characteristics are shown in Table 1.

Presentation of local recurrence and surgical procedures

The interval between resection of the primary rectal cancer and surgery for local recurrence was a median of 24 (range, 4–113) months. All of the laparotomies were undertaken with the intention of a curative resection. Abdominoperineal excision of rectum was performed in 19 patients, palliative surgery such as colostomy or biopsy in 14, non-anatomic resection in 13, pelvic exenteration in three and low anterior resection was possible in one patient. Palliative surgery was performed in 14 of 50 patients. Three of these patients had carcinomatosis. Three patients had involvement of the sacrum, the relatives of two of them did not accept composite resection, the remaining patients involved sacrum that extended further proximally than had been anticipated on preoperative imaging; S1 was infiltrated with tumor. The remaining eight patients had a large fixed pelvic mass and they were found to have unresectable disease or found to have extrapelvic metastasis. The recurrent tumors were classified as not fixed (F0) in 27 patients, fixed at one site (F1) in seven and fixed to two or more sites (F2) in 16 patients. Details of locally recurrent tumors and the operations performed are shown in Tables 1 and 2.

Predictors of curative resection

Thirty-six patients who had curative resection with removal of all gross disease were identified. On final pathologic analysis of the resected specimen, 12 of these patients were found to have a microscopically positive resection margin (R1). Therefore, the 50 patients in the group of LRRC included 24 patients with a margin negative (R0) resection. R1 resection was mostly seen in seven patients (56%) with non-anatomic resections which they had undergone to the APR previously (Table 2). Primary procedure (sphincter preserving surgery) has affected the availability of curative resections, p-value was significant statistically ($p = 0.002$). Table 3 compares the characteristics of patients who underwent curative and palliative resections. In accordance with our data, bleeding ($p = 0.012$), anastomotic localization ($p = 0.001$), F0 fixation ($p < 0.0001$) and low CEA ($p = 0.02$) has significant effect on possibility of curative resection. The interval between resection of the primary tumor and surgery for local recurrence did not have any effect on the availability of curative resections ($p = 0.195$).

Operative morbidity and symptom control

There was no operative mortality among the 50 patients. A total of 15 complications occurred in 12 patients. Seven

Table 2
Surgical procedures and residual tumor status

	R0	R1	R2
APR	14	5	–
Palliative surgery	–	–	14
Non-anatomic resection	6	7	–
Pelvic exenteration	3	–	–
Low anterior resection	1	–	–
Total	24	12	14

R0 = negative margin resection; R1 = microscopically positive surgical margin; and R2 = gross residual disease.

Table 3
Factors affecting the nature of resection for local recurrence

Factor	Curative	Palliative		*p*-Value
	R0	R1	R2	
No. of patients	24	12	14	
Sex				
Male	16	9	8	
Female	8	3	6	0.63
Mean age	55.6 (35–77)	55.2 (34–79)	51.7 (26–71)	0.12
Initial operation				
APR	3	3	11	
Non-APR	21	9	3	0.001
Location of primary tumor				
Circumferential	15	6	10	
Lateral	1	1	–	
Anterior	4	4	4	
Posterior	4	1	–	0.52
Primary T stage				
T1/2	5	1	1	
T3/4	19	11	13	0.41
Primary N status				
N0	11	6	4	
N1/2	13	6	10	0.47
Primary resection margins				
Negative	18	9	9	
Positive	6	3	5	0.75
Presentation of recurrent tumor (symptoms)				
Pain	8	7	11	
Hemorrhage	16	5	3	0.02
Recurrent tumor location				
Composite (pelvic)	1	1	14	
Sidewall (lateral)	3	–	–	
Central (anastomosis)	18	9	–	
Sacral (posterior)	2	2	–	<0.0001
Fixity				
F0	18	9	–	
F1	5	2	–	
F2	1	1	14	<0.0001
Hydronephrosis				
No	22	12	9	
Yes	2	–	5	0.24
Increase in CEA				
No (CEA < 4)	11	3	1	
Yes (CEA > 4)	13	9	13	0.04
Median time to recurrence (months)	19 (9–113)	24 (4–56)	23 (8–38)	0.12
Median survival (months)	28 (12–81)	12 (3–42)	6 (3–23)	0.000

of the 24 patients who had curative resection had complications, compared with 5 of 26 of those who had palliative resection ($p = 0.45$). The complications, more than half of which were pelvic collections (two patients), intestinal obstruction (three patients), and urologic problems (three patients). Three patients required operative treatment for the complications, including one operation for intestinal obstruction, one for postoperative hemorrhage, and one for a pelvic abscess. Symptom free survival was determined for the examined symptoms (bleeding, pain, and fistula) from the time of surgery for LRRC. Median symptom free survival times were significantly shorter in patients undergoing palliative operations (5 months) compared with those who had nonpalliative procedures (15 months; $p = 0.01$). Statistical analysis showed that the presence of gross disease (R2) after surgery, pain at the time of recurrent surgery were associated with a worse symptom free survival in all patients ($p = 0.01$).

Survival after curative resection

We evaluated primary characteristics of patients, clinical and histological parameters to predict the survival in patients with locally recurrent rectal cancer. Overall survival of the whole group of patients was 19 (range, 3–81) months. In the survival analysis, previous surgery and curative surgery were significant predictors of both disease-specific survival and overall survival. The CEA level at the time of recurrent disease was also significant predictor of overall survival ($p = 0.004$). The median survival of curative (R0), R1 and R2 resections were 28, 12, and 6 months, respectively ($p < 0.0001$). The effect of primary surgery and the effect of surgical margin are shown in Figs. 1 and 2, respectively. Age, gender, primary resection margin, primary T stage and N status, symptoms, fixation and location of recurrent tumor did not have any impact on survival.

Of the 24 patients who had curative resection, eight have remained disease-free for 21–69 months. Of 16 patients with subsequent recurrent disease, local recurrence alone in pelvis was seen in three patients, distant metastasis in eight patients, and a combination of both in five patients. Median time to a second recurrence (pelvic, distant or both) was 20 (range, 10–70) months after curative resection of LRRC. Distant metastases occurred in one or more sites (in 13 patients, liver $n = 7$, lung $n = 5$, bone $n = 3$, brain $n = 3$) after curative surgery for local recurrence and these metastases were accepted unresectable. Patients who developed a second local recurrence (pelvic recurrence with or without extrapelvic disease, $n = 8$) did so with a median time to recurrence of 18 (range, 10–30) months, and thus local control was 67%. Of two patients with pelvic recurrence without extrapelvic disease had unresectable disease in pelvis, the remaining patient was operated with pelvic exenteration for second local recurrence. This patient is still alive without recurrence for 10 months.

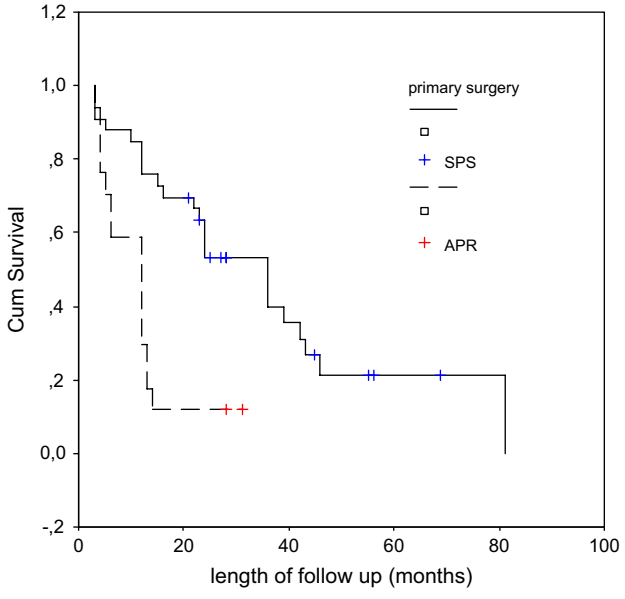

Figure 1. Survival of patients who performed sphincter preserving surgery (SPS) compared with abdominoperineal resection (APR) ($p = 0.025$).

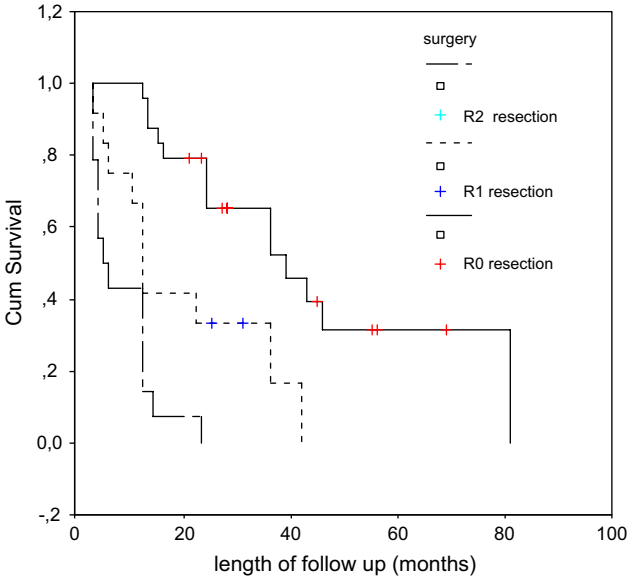

Figure 2. Comparison of survival of patients who underwent curative and palliative resection for local recurrence ($p < 0.0001$).

Disease-free survival for this cohort of 50 patients was 16 months, with statistically significant differences observed in the long-term prognosis of patients with curative vs non-curative resections ($p < 0.0001$).

Discussion

Curative resection and influencing factors

Management of the isolated locoregional recurrence is a therapeutic challenge. A selective group of patients with LRRC can be operated on with curative intent and can result in long-term survival benefits. Curative surgical approach can be achieved only when microscopic margins are negative. This can be achieved in about 45% of cases, ranging from 10% to 67% in the published literature.[14–18] Negative resection margins were achieved in 48% of the patients in our series. The curative resection rate depends on many factors. Gender and age had no effect on the probability of a curative resection in our analysis, but some authors demonstrated that female gender was to be a factor associated with higher probability of performing curative surgery.[3,19] The increased probability of a curative resection may be related to the different structure of the female pelvis, which allows for easier surgical access and a better follow-up due to the anterior spread of the tumor to the vajinal wall and uterus.

Apart from the primary surgery, localization, T stage, N status and resection margin of primary tumor and recurrence time are not to be factors associated with higher probability of curative surgery. Abdominoperineal resection at

the time of initial surgery does not allow for an easier curative second surgery. Early diagnosis of local recurrence after sphincter preserving operation is facilitated by surveillance digital rectal examination, sigmoidoscopy, and symptoms of bleeding or changes in bowel habit, whereas the majority of local recurrences after APR are diagnosed after detection of elevated CEA levels or pelvic pain.[12,20] When the rectum surgically absent, recurrent pelvic tumors are quick to invade neighboring structures such as the sacrum or the ureters.[16,17,20] This is not so common when the rectum has been reconstructed and should be less so when the native rectum is preserved after local excision.[12,17,20–24]

The symptoms, localization and fixity of recurrent cancer were significantly associated with the probability of curative resection. Valentini et al.[24] found that the extent of pelvic recurrence fixation along the pelvic sidewall predicted a worse local control and overall survival rate. The impact of fixation on curative resection and overall outcome has been demonstrated in another recent study.[12] Hahnloser et al.[12] demonstrate that the degree of fixation of the local recurrence in the pelvis was the most significant prognostic indicator for palliative surgery and overall survival. Survival for the main prognostic factor within that group were 43%, 24%, 20%, and 0% for nonfixed (F0), F1, F2, and F3 recurrent tumors, respectively. In the other hand, higher complication rates were observed in patients whose recurrence was fixed in more than two sites in the pelvis. Two or more sites of fixation were associated with a significantly worse outcome compared with mobile tumors or those with only one site of fixation. Increased number of sites of fixation was indicative of a more advanced local tumor recurrence, made surgery difficult.[25,26] As well as degree of fixation, symptomatic pain and peripheral tumor location another variables associated with the presentation of local recurrence, were also significantly predictive for curative or palliative resection in the current study, but not for long-term survival.

Survival and influencing factors

Some studies have analyzed factors that affect the survival of patients after resection of LRRC. The possibility of performing curative resection has been consistently reported to be a significant determinant of survival. The reported median survival varies from 17 to 50 months after obtaining R0 resection with or without IORT.[6,19,23,27–31] Statistical significance was demonstrated in almost all reports published in the literature. The survival is greatly increased when a resection with microscopically negative margins can be performed. While the validity of an R0 resection is well known, there is no agreement about the differences between an R1 and an R2 resection: in three out of four reports no difference was seen relative to this parameter. In this sense, the report of Wiig[30] showed quite different data: no statistical difference between R0 and R1 resection − also shown by Salo[20] − and highly statistical difference between R1 and R2 resection. However, the amount of residual disease following maximal surgical resection had an important impact on long-term survival in this study. Surgical margin following resection of recurrence was confirmed as having the most significant influence on survival. In our study of resection of local recurrence in 50 patients, curative resection was possible in 48%. Of the patients who had curative resection, 33% of these patients remained disease-free for median 37 months. Local recurrence alone was seen in 12.5%, distant metastasis in 33%, and a combination of both in 21%. Being able to perform curative resection is the most significant factor for local and systemic failure and survival.

One of the other factors that affect the survival of patients was initial surgery. Patients who had resection of local recurrence after APR for primary tumor had lower survival than those who had primary sphincter preserving surgery (Fig. 1). A number of series have reported similar results.[17,20,23–25] The surgeons' technical skills and attitude may have more influence on important factors, including surgical margin status and complications, in LRRC surgery. Extensive surgery should thus be undertaken in specialized centers that have an experienced complex-treatment team.[32] Especially, in the case of APR, detection of pelvic recurrence is not easy; and resection usually involves extensive procedures. Thus resection of local recurrence usually involves major surgery with removal of adjacent pelvic organs. Operative morbidity varies from 22% to 100%.[3,13,17] The morbidity rate varies with the magnitude of the surgery. Wanebo et al.[21] described the use of pelvic exenteration for advanced tumors, and a resection rate of 88% was reported. Though 50% 3-year survival was achieved, postoperative mortality was as high as 9%, and the morbidity was nearly 100%. In our series, 40% of patients ($n = 20$) required extended resection with excision of other pelvic organs. There was no perioperative mortality in the whole series, and the overall complication rate was 24%, which compares favorably with others' results.[13,22,25] In addition, reoperation for LRRC may be associated with substantial mortality and morbidity.[32] As a practical matter, however, the extent of recurrent pelvic tumor (second local recurrence) and the frequent need for multivisceral resection preclude extensive surgical resections from being considered as palliative procedures in patients with liver, lung, or peritoneal metastases because of their expected short survival duration. In this presented study, distant metastases occurred in one or more sites after curative treatment for local recurrence in 13 of 24 patients (54%). In three patients, second isolated local recurrence (pelvic recurrence without distant metastases) was developed, two of them had unresectable disease in pelvis, the remaining patient was operated with pelvic exenteration for second local recurrence. This patient is still alive without recurrence. We think that an aggressive surgical approach offers patients with LRRC the best potential survival. However, careful patient selection is important for surgery to impart a survival benefit.

Influence of radiotherapy

Recent advances in conformal radiotherapy techniques, including the use of intensity modulated radiotherapy (IMRT – alone or combined with chemotherapy),[24,33–35] intraoperative radiotherapy (IORT),[12,13,36–38] and postoperative brachytherapy[39] has allowed re-radiation of patients with local recurrence to an additional dose of 30–40 Gy. In Hahnloser's study,[12] IORT was applied selectively in 52% and 33% of patients with palliative or curative surgery and achieved good 5-year survivals (21% and 27%, respectively). The multimodality approach and the specific results of local control with IORT, it seems reasonable to continue this practice of combined therapies but unfortunately IORT is not available in most of the center as like as our institution.

Conclusion and recommendation

Until today, determining the therapeutic algorithmic approach for LRRC is still conflicting. The main reasons for this include fixity, performed initial surgery, lack of studies and group heterogeneity, differences in surgical procedures ranging from APR to pelvic exenteration and sacral resections and the availability of techniques such as IORT among surgical centers. These nonhomogen changing parameters make it difficult to formulate as algorithm for treatment modality. However, with the comprehend that patients with LRRC are treatable, the goal is to obtain R0 resection. Longer survival rates can be achieved when R0 resection is obtained.

In our experience, R0 resection is more easily obtained in patients with symptoms of bleeding, especially ones that are localized to the anastomosis with less fixation to surrounding structures, and patients who have had sphincter preserving surgery for primary tumor. These are better candidates for surgery. We believe that with the proper selection of surgical candidates and in experienced hands can contribute greatly to a more favorable outcome.

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