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Predictors of Recurrence After Local Excision and Postoperative Chemoradiation Therapy of Adenocarcinoma of the Rectum

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Background: Local excision of rectal cancer preserves anal continence, bladder function, and normal sexual function. However, local recurrence after excision remains a significant problem. To further define the indications for local excision, we analyzed possible factors predictive of recurrence after local excision of rectal cancer.

Methods: The charts of all patients undergoing local excision of adenocarcinoma of the rectum between 1985 and 1995 at a single institution were reviewed. Patients with metastatic disease at the time of excision and patients treated preoperatively with chemoradiation therapy were excluded. All available slides were reviewed by a single pathologist, who assessed the depth of invasion; the presence or absence of vascular invasion, lymphatic invasion, perineural invasion, and lymphocytic infiltrate; the mucinous status; and the degree of differentiation. Using the log-rank test and Cox proportional hazards model, univariate and multivariate analyses were performed to identify predictors of recurrence.

Results: Ninety patients underwent local excision, 46 transanally and 44 using a Kraske approach. The breakdown of patients by tumor stage was as follows: Tis, 13%; T1, 41%; T2, 30%; T3, 15%; and Tx, 1%. Sixty-eight percent of patients with T1 tumors were treated with postoperative radiotherapy; all patients with T2 or T3 tumors were treated postoperatively with or without 5-fluorouracil. The median duration of follow-up was 51 months. The median tumor diameter was 2.5 cm (range, 0.4 to 7 cm), and the median distance of the tumor from the anal verge was 4.5 cm (range, 1 to 10 cm). The 4-year actuarial local disease-free survival rate broken down by tumor stage was as follows: Tis, 100%; T1, 95%; T2, 80%; and T3, 73%. The median time to local recurrence was 23 months (range, 7 to 61 months). Multivariate analysis showed that only tumor stage and margin status were predictors of local recurrence.

Conclusions: Local excision and postoperative radiotherapy result in adequate local control of early stage (Tis and T1) adenocarcinoma of the rectum. Higher rates of recurrence were seen in patients with T2 and T3 tumors, especially in those with positive margins.

Key Words: Rectal cancer—Local excision—Radiotherapy.

Adenocarcinoma of the low rectum traditionally has been treated with abdominoperineal resection (APR).[1] However, a permanent colostomy must be created in such patients, and impotence and bladder dysfunction are possible neurogenic complications of the procedure. As a result of recent technical improvements in pelvic surgery and the addition of adjuvant chemoradiation therapy to the treatment regimen, sphincter-sparing procedures often can be used rather than APR. The least invasive of these procedures is local excision performed transanally or transsacrally.

In the past, local excision was performed only if the patient was in poor medical condition or refused to have a colostomy. More recently, local excision has been performed with curative intent to remove well-differentiated lesions that are less than 3 cm in diameter and are limited to the mucosa or submucosa.[2–5] However, tumors have been observed to recur after local excision.[6] To

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further define the indications for local excision of low rectal cancer, we attempted to identify predictors of recurrence after local excision of rectal adenocarcinoma.

PATIENTS AND METHODS

We reviewed the charts of all patients with histologically proven adenocarcinoma of the rectum who were treated with local tumor excision at The University of Texas M. D. Anderson Cancer Center between 1985 and 1995. Patients with metastatic disease at the time of local excision were excluded from the analysis, as were patients treated preoperatively with chemoradiation therapy. Ninety patients who met the inclusion criteria were identified.

All available slides were reviewed by a single pathologist (KRC), who determined the depth of invasion; the presence or absence of vascular invasion, lymphatic invasion, perineural invasion, and the lymphocytic infiltrate; the mucinous status; and the degree of differentiation. The primary tumor was staged according to the American Joint Committee on Cancer staging system[7] as follows: Tis, carcinoma in situ; T1, tumors invading the submucosa; T2, tumors invading the muscularis propria; and T3, tumors invading the perirectal fat. Transrectal ultrasonography was used to assess the depth of invasion and nodal status primarily, starting in 1990.

Patients with in situ carcinoma had no further therapy after surgical excision. In the first 5 years of the series, patients with T1 tumors received radiotherapy postoperatively, but starting in 1990, radiotherapy was used more selectively in such patients because of the low local recurrence rates in this subgroup.[3] Sixty-eight percent of patients with T1 lesions and all patients with T2 or T3 lesions received radiotherapy postoperatively. Radiotherapy was started 4 to 6 weeks after the incision had healed and anal continence had returned to normal. Patients were treated on an open-top table (belly-board technique) to mobilize the small bowel out of the field. Treatment portals consisted of posterior and right and left lateral treatment fields; 50% of the dose was prescribed to the posterior field and 25% of the dose was given through each lateral field. Radiation dose homogeneity was achieved by using 45-degree wedges over the lateral radiation fields. 5-Fluorouracil was given Monday through Friday during radiotherapy by continuous infusion (300 mg/m^2/day) in 12 patients. A total radiation dose of 53 Gy to the surgical bed was prescribed. The initial radiation field included the primary tumor site with margin and the pelvic lymph nodes. A total of 45 Gy was administered to the pelvis over 25 fractions at 1.8 Gy/day, with dose specified to the 95% isodose curve. After 45 Gy, radiation treatment fields were reduced to treat an area of 3 to 5 cm around the primary tumor site. This boost field received an additional 8 Gy over four fractions at 2 Gy/day, with dose specified to the 95% isodose curve.

Patients were followed up at 3- to 6-month intervals after operation. Evaluation consisted of physical examination, proctoscopy, and chest radiography. Local recurrence was defined as recurrence at the site of resection (mural) or in the perirectal lymph nodes (perirectal). Distant recurrence was defined as disease in distant organs. Median follow-up in survivors was 51 months.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS, Inc, Evanston, IL). Kaplan-Meier survival analysis methods were used. The end points were time to local recurrence (local disease-free survival) and time to any recurrence (disease-free survival). Univariate and multivariate analyses were performed using the log-rank test.

RESULTS

There were 46 men and 44 women (Table 1). The median age was 62 years (range, 28 to 88 years). Lesions

TABLE 1. *Patient and treatment characteristics (n = 90)*

Characteristic	No. patients (%)
Sex	
Male	46 (51)
Female	44 (49)
Procedure	
Transanal excision	46 (51)
Kraske resection	44 (49)
Margins*	
Negative	73 (81)
Close (≤1 mm)	8 (9)
Positive	5 (6)
Radiation	
None	25 (28)
Postoperative	65 (72)
T stage	
Tis	12 (13)
T1	37 (41)
T2	27 (30)
T3	13 (14)
Unknown	1 (1)
N stage	
N0	56 (62)
N1	5 (6)
Ultrasonography not done	29 (32)
Grade	
Villous adenoma	12 (13)
Well differentiated	11 (12)
Moderately differentiated	55 (61)
Poorly differentiated	8 (9)
Unknown	4 (4)

* Margin status could not be determined in 4 patients.

were located 1 to 10 cm (median, 4.5 cm) from the anal verge, with 75% of lesions 6 cm or less from the anal verge. Forty-six patients underwent transanal excision, and 44 underwent a Kraske resection. Surgical margins were negative in 81 patients (90%), whereas margins were microscopically positive in 5 patients (6%). Margin status could not be assessed in four patients.

The median tumor diameter was 2.5 cm (range, 0.4 to 7 cm). Twelve patients (13%) had carcinoma in situ, 37 patients (41%) had T1 lesions, 27 patients (30%) had T2 lesions, 13 patients (15%) had T3 lesions, and the depth of invasion could not be accurately assessed on pathology in 1 patient. Sixty-one patients (68%) underwent transrectal ultrasonography preoperatively; it revealed positive lymph nodes in five patients. Most tumors were well or moderately differentiated; only eight patients had poorly differentiated tumors. In the patients for whom slides were available, lymphatic invasion was identified in 21 patients (34%), vascular invasion in 9 patients (15%), perineural invasion in 4 patients (7%), and lymphocytic infiltrate in 10 patients (18%; Table 2). Eight patients (10%) had mucinous adenocarcinomas.

Complications occurred more often in the patients treated with a Kraske resection ($P = .0003$; Table 3). The most common complication was the formation of a fistula, which necessitated a temporary diverting colostomy in six patients. Although most patients had no incontinence, six patients (7%) had occasional episodes of incontinence, and one patient had complete incontinence. There were no deaths related to surgery.

TABLE 2. *Tumor characteristics (n = 62)*

Characteristic*	No. patients (%)
Lymphatic invasion	
Yes	21 (34%)
No	41 (66%)
Vascular invasion	
Yes	9 (15%)
No	53 (85%)
Perineural invasion	
Yes	4 (7%)
No	54 (93%)
Lymphocytic infiltrate	
None	48 (83%)
1+	8 (14%)
2+	2 (4%)
Mucinous adenocarcinoma	
Yes	8 (10%)
No	70 (90%)

* Not all slides were available for review.

TABLE 3. *Complications after transanal or Kraske resection for rectal carcinoma*

Complications	No. patients (%)	
	Transanal (n = 46)	Kraske (n = 44)
Fistula	1 (2%)	7 (16%)
Wound dehiscence	0	3 (6%)
Infection	0	1 (2%)
Bowel perforation	1 (2%)	0
Stricture	0	1 (2%)
Complete incontinence	0	1 (2%)
Total	2 (4%)*	13 (29%)*

* $P = .0003$, χ^2 analysis.

Patterns of Recurrence

Disease recurred in 17 patients. The recurrences were local in five patients, distant only in six patients, and combined in six patients (Fig. 1). Five of the local recurrences were mural, and six were perirectal. Four of the five patients with local recurrence have undergone APR and are alive without disease; the fifth patient has undergone repeated fulguration of her recurrent tumor because of comorbid conditions.

Distant metastases developed after local disease in five of the patients with combined recurrences. The sixth patient underwent liver resection to remove metastatic tumor 10 months after the initial local excision and then

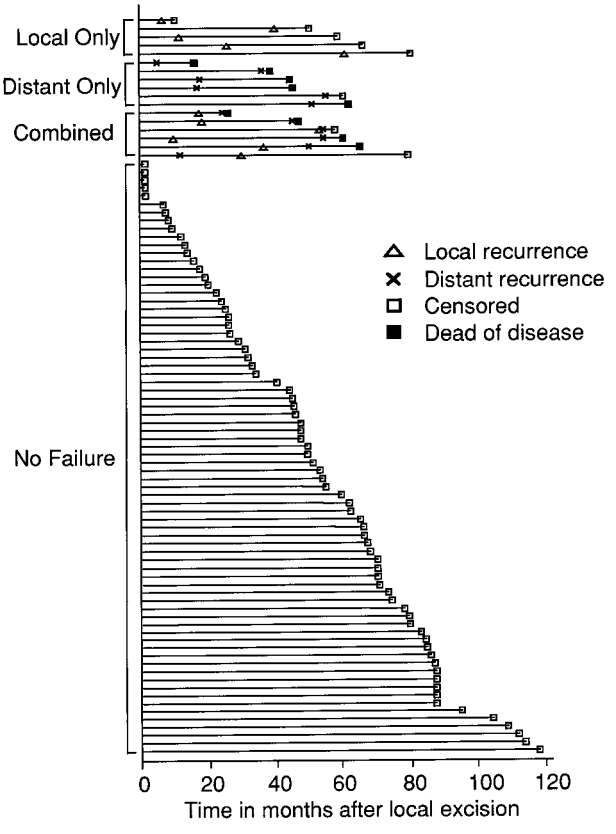

FIG. 1. Patterns of failure after local excision of rectal adenocarcinoma.

APR to remove locally recurrent tumor 23 months after the initial local excision. He is currently alive without evidence of disease 80 months after the first operation.

Five of the six patients with distant recurrence only are dead of disease; the sixth is alive with disease.

Local Recurrence

During a median follow-up of 51 months, disease recurred locally in 12% of the 90 patients. The median time to local recurrence was 23 months (range, 7 to 61 months). Local control was achieved in all patients with in situ tumors (Table 4). The 4-year actuarial local DFS rate was 95% in patients with T1 lesions, 80% in patients with T2 lesions, and 73% in patients with T3 lesions (Fig. 2*A*). Univariate analysis revealed that disease was more likely to recur in patients with positive margins than in those with negative margins, T2 or T3 lesions were more likely to recur than were Tis or T1 lesions, and tumors 4 cm or larger were more likely to recur than were those less than 4 cm in diameter (Table 5). Lymphatic, vascular, and perineural invasion; a lymphocytic infiltrate; histologic grade; and mucinous differentiation did not prove to be significant predictors of local recurrence. On multivariate analysis, only the tumor (T) stage and margin status proved to be significant predictors of local recurrence (Table 6).

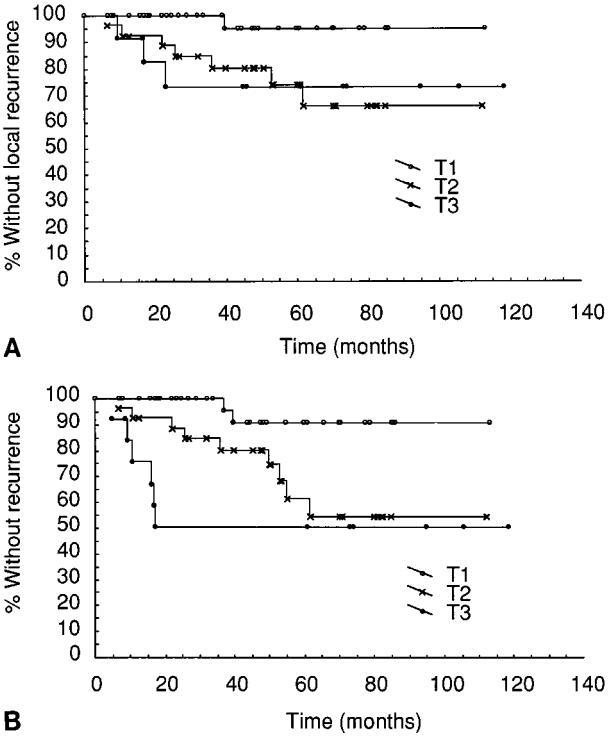

FIG. 2. (**A**) Local disease-free survival by T stage. (**B**) Disease-free survival by T stage.

Disease-free Survival and Disease-specific Survival

The overall DFS rate was 82%. The 4-year actuarial DFS rate was 91% in patients with T1 lesions, 80% in patients with T2 lesions, and 50% in patients with T3 lesions (Fig. 2*B*). The overall disease-specific survival rate was 90%. The 4-year actuarial DSS rate was 95% in patients with T1 lesions, 89% in patients with T2 lesions, and 67% in patients with T3 lesions. On univariate analysis, positive margins, T2 or T3 lesions, positive lymph nodes, mucinous differentiation, and tumors 4 cm or more in diameter were significant negative prognostic factors for DFS. In contrast, lymphatic, vascular, and perineural invasion; a lymphocytic infiltrate; and histologic grade were not significant prognostic factors for DFS. On multivariate analysis, the T stage, margin status, and mucinous status were significant prognostic factors for DFS.

TABLE 4. *Actuarial 4-year local disease-free survival, disease-free survival, and disease-specific survival after local excision of rectal cancer according to T stage*

T stage	LDFS	DFS	DSS
Tis	100%	100%	100%
T1	95%	91%	95%
T2	80%	80%	89%
T3	73%	50%	67%
Overall	87%	82%	90%

DFS, disease-free survival; DSS, disease-specific survival; LDFS, local disease-free survival.

DISCUSSION

Recent data suggest that the combination of local excision and postoperative chemoradiation therapy may be an option for some patients with early-stage rectal cancer. This was shown in a recent phase II intergroup study in which local excision of a distal rectal cancer was attempted in 180 patients.[8] Patients with involved margins or tumors that were more than 4 cm in diameter, higher than T2, and less than T1 were declared ineligible. Of the remaining 113 patients, 60 patients with T1 disease received no further treatment, and 53 patients with T2 disease were treated with external beam radiation plus 5-FU. After a median follow-up of 24 months, only two patients had isolated local recurrences, and both had undergone resection and were alive. Although these results in a very select group of patients are encouraging, our data suggest that longer follow-up is necessary to identify those patients who will have recurrence, as shown by the fact that the median time to local recur-

TABLE 5. *Univariate analysis of risk factors for local recurrence and disease-free survival after local excision of rectal adenocarcinoma*

Variable	No. patients	Local DFS		DFS	
		P	HR (CI)	*P*	HR (CI)
Sex (female vs. male)	90	.64	1.33 (0.14–4.37)	.33	0.61 (0.22–1.65)
Type of surgery (Kraske vs. transanal)	90	.47	1.57 (0.46–5.40)	.15	2.14 (0.75–6.09)
T2 vs. T1	77	.04	8.6 (1.06–69.94)	.03	5.45 (1.18–25.22)
T3 vs. T1	77	.06	8.5 (0.9–81.6)	.01	8.85 (1.78–43.96)
N1 vs. N0	61	.64	1.65 (0.20–13.70)	.06	3.47 (0.95–12.66)
Margin status	86	.04	5.40 (1.10–26.07)	.0001	14.25 (3.95–51.40)
Lymphatic invasion	62	.98	1.02 (0.25–4.08)	.57	1.35 (0.48–3.80)
Vascular invasion	62	.49	1.73 (0.37–8.17)	.99	1.01 (0.23–4.50)
Perineural invasion	58	—	—	.71	1.47 (0.19–11.30)
Lymphocytic infiltrate	58	.43	0.43 (0.05–3.48)	.41	0.53 (0.12–2.40)
Mucinous	78	.98	1.02 (0.13–8.01)	.02	3.80 (1.23–11.74)
Grade (well vs. moderately differentiated)	76	.39	2.49 (0.32–19.45)	.20	3.72 (0.49–28.21)
Size	78	.05	1.44 (1.00–2.05)	.04	1.36 (1.01–1.82)

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; LDFS, local disease-free survival.

TABLE 6. *Multivariate analysis of risk factors for local recurrence and disease-free survival after local excision of rectal adenocarcinoma*

Factor	Local DFS		DFS	
	P	HR (CI)	*P*	HR (CI)
T stage (T2–3 vs. T1)	.03	32 (1.3–8.22)	.01	7.3 (1.5–35.6)
Margin (positive vs. negative)	.01	14 (1.7–114)	.04	7.8 (1.1–57.2)
Age	.62	1.0 (0.9–1.1)	.21	(1.0 (0.9–1.1)
Radiation therapy (yes vs. no)	.10	0.05 (0.0–1.8)	.06	0.05 (0.0–1.2)
Grade (moderately/poorly vs. well differentiated)	.32	4.1 (0.24–72)	.25	4.3 (0.4–51.5)
Sex (female vs. male)	.75	1.3 (0.3–4.9)	.17	0.4 (0.1–1.4)
Procedure (KR vs. TA)	.84	0.8 (0.2–3.5)	.81	1.1 (0.3–3.8)
Mucinous (yes vs. no)	.56	1.9 (0.2–17.1)	.05	4.8 (0.9–24.0)

CI, confidence interval; HR, hazards ratio; KR, Kraske, TA, transanal.

rence in our study was 23 months, with a range of 7 to 61 months.

The T stage appears to be the most important predictor of recurrence after local excision of rectal cancer. In line with this, Minsky et al.[9] at the Memorial Sloan-Kettering Cancer Center reported that as the T stage increased, the incidence of local failure also increased (T1, 0%; T2, 17%; and T3, 33%) and DFS decreased (T1, 100%; T2, 67%; and T3, 50%). These authors concluded that although other clinicopathologic factors may be involved, the T stage is the most reliable predictor of local recurrence and DFS in patients with rectal cancer who undergo local excision and postoperative radiotherapy. This was also borne out by our study, in which the actuarial 4-year local recurrence rates were similar (T1, 5%; T2, 20%; and T3, 27%). Our findings further underscore the importance of an early T stage in candidates for local excision of rectal cancer.

Lymph node metastases are seen in 12% of patients with T1 lesions, 22% of patients with T2 lesions, and 58% of patients with T3 and T4 lesions.[10] Data from several centers suggest that the standard treatment for patients with lesions of stage T3 or higher is total mesorectal excision.[11–13] Because local excision does not include total mesorectal excision, it is therefore unlikely that local excision will be adequate in patients with more advanced rectal cancer unless chemoradiation therapy can reliably sterilize nodal basins. One way to determine the likelihood of positive perirectal lymph nodes before treatment is to perform transrectal ultrasonography or pelvic computed tomography. If positive nodes are identified by these means, lymphadenectomy is indicated and the patient therefore is not a candidate for local excision.

Tumor-free margins and full-thickness tumor excision also are critical for preventing local recurrence and thereby ensuring a successful outcome. This was pointed out in a study at New England Deaconess Hospital in which tumor was found to recur locally in 56% of patients with positive margins who underwent local excision and postoperative irradiation.[14] In our study, pos-

itive margins were found to be a predictor of recurrence of rectal cancer. Specifically, multivariate analysis showed that disease was more likely to recur locally in patients with positive margins. To achieve an adequate excision, the site should be properly exposed and the tumor should be small. Lesions in the upper or middle third of the rectum often are not amenable to transanal approaches and are best excised using a low anterior resection. Circumferential lesions are difficult to excise locally and achieve negative surgical margins. A negative radial margin also may be difficult to achieve in the event of a T3 lesion that has invaded the perirectal fat or anal sphincter. If a negative margin cannot be achieved, the patient is not a good candidate for local excision.

The impact of other clinicopathologic features of the primary tumor on prognosis is still unclear. Some investigators have found that blood vessel invasion, lymphatic invasion, perineural invasion, and lymphocytic infiltrate are poor prognostic indicators;[15–17] others have not, however.[9,18] Lymphatic invasion also has been found to be an independent, although weaker, prognostic factor than venous invasion and is associated with higher rates of recurrence and decreased survival, particularly in patients with stage III tumors.[19] In practice, however, it may be difficult to discriminate among retraction artifact, lymphatic invasion, and vascular invasion without performing elastic tissue staining or immunohistochemical staining for endothelial cells. Such special staining to distinguish reliably between venous and lymphatic invasion actually has been done in only a few studies,[17] so claims made on the basis of findings in studies in which such special staining has not been done are not necessarily well founded. Patients whose tumors show neural invasion appear to have shorter survival, but this finding usually accompanies other features of advanced disease, which can be confounding factors.[17] In our study, lymphatic invasion, vascular invasion, perineural invasion, and lymphocytic infiltrate did not significantly predict outcome.

Several studies have shown that a large extracellular mucinous component in colorectal adenocarcinomas predicts recurrence.[20,21] For example, in a review from the Ochsner Clinic, it was noted that mucinous carcinomas of the rectum occurred at an advanced stage more often than nonmucinous rectal carcinomas did and that they were associated with a markedly worse 5-year survival.[21] Similar findings were made at The University of Texas M. D. Anderson Cancer Center.[20] In addition, multivariate analysis of the data in our study showed positive mucinous status to be a significant predictor of a worse DFS rate ($P = .05$).

In summary, although other clinicopathologic features may have an impact on prognosis, T stage and positive tumor margins remain the most reliable predictors of local recurrence and DFS in patients with rectal cancer who undergo local excision and postoperative radiotherapy. Our data show that Tis or T1 tumors of the rectum can be adequately treated with local excision. Patients with T1 tumors without adverse pathologic factors have a low enough incidence of local failure and positive nodes that they do not require adjuvant radiotherapy. However, local excision is not appropriate for the removal of T2 or T3 tumors, especially those for which negative margins cannot be achieved, and those shown by ultrasonography to be associated with positive nodes. Such patients should be treated with either APR or sphincter-sparing proctectomy with coloanal anastomosis in most circumstances, given the reports of a high degree of local control in patients who undergo total mesorectal excision and appropriate adjuvant treatment. In selected circumstances, however, (e.g., informed patient decision, extensive comorbid disease, or distant metastases) local excision can be successful. Improved clinical staging systems, together with careful histologic and biologic analyses of various phenotypic markers, may enable us to identify those patients with rectal cancer who are the best candidates for local excision.

REFERENCES

1. Cohen AM, Minsky BD, Schilsky RL. Cancer of the rectum. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practices of Oncology.* 5th ed. Philadelphia: Lippincott-Raven, 1997:1197–1233.
2. Ellis LM, Mendenhall WM, Bland KI, Copeland EM. Local excision and radiation therapy for early rectal cancer. *Am Surg* 1988; 54:217–20.
3. Ota DM, Skibber JM, Rich TA. M. D. Anderson Cancer Center experience with local excision and multimodality therapy for rectal cancer. *Surg Oncol Clin North Am* 1992;1:147–52.
4. Biggers OR, Beart RW, Ilstrup DM. Local excision of rectal cancer. *Dis Colon Rectum* 1986;29:374–7.
5. Coco C, Magistrelli P, Granone P. Conservative surgery for early cancer of the distal rectum. *Dis Colon Rectum* 1992;35:131–6.
6. Baron PL, Enker WE, Zakowski MF, Urmacher C. Immediate vs. salvage resection after local treatment for early rectal cancer. *Dis Colon Rectum* 1995;38:177–81.
7. Beahrs OM, Henson DE, Hutter RVP, Kennedy BJ. American Joint Committee on Cancer. *Colon and Rectum.* Philadelphia: Lippincott-Raven, 1997:83–90.
8. Steele GD, Herndon JE, Burgess AM, et al. Sphincter sparing treatment for distal rectal adenocarcinoma: a phase II intergroup study (abstract). *Proc Am Soc Clin Oncol* 1997;16:256.
9. Minsky BD, Enker WE, Cohen AM, Lauwers G. Clinicopathologic features in rectal cancer treated by local excision and postoperative radiation therapy. *Radiat Med* 1995;13:235–41.
10. Brodsky JT, Richard GK, Cohen AM, Minsky BD. Variables correlated with the risk of lymph node metastasis in early rectal cancer. *Cancer* 1992;69:322–6.

11. Heald R. Total mesorectal excision is optimal surgery for rectal cancer: a Scandinavian consensus. *Br J Surg* 1995;82:1297–9.
12. Enker WE, Havenga K, Polyak T, Thaler H, Craner M. Abdominoperineal resection via total mesorectal excision and autonomic nerve preservation for low rectal cancer. *World J Surg* 1997;21:715–20.
13. Skibber JM. Advances in rectal cancer treatment. *Cancer Treat Res* 1997;90:29–49.
14. Rich TA, Weiss DR, Mies C, Fitzgerald TJ, Chaffey JT. Sphincter preservation in patients with low rectal cancer treated with radiation therapy with or without local excision or fulguration. *Radiology* 1985;156:527–31.
15. Chapuis PH, Dent OF, Fisher R, Newland RC, Pheils MT, Smyth E, Colquhoun K. A multivariate analysis of clinical and pathological variables in prognosis after resection of large bowel cancer. *Br J Surg* 1985;72:698–702.
16. Harrison JC, Dean PJ, el-Zeky F, Vander Zwaag R. From Dukes through Jass: pathological prognostic indicators in rectal cancer. *Hum Pathol* 1994;25:498–505.
17. Krasna MJ, Flancbaum L, Cody RP, Shneibaum S, Ben Ari G. Vascular and neural invasion in colorectal carcinoma. Incidence and prognostic significance. *Cancer* 1988;61:1018–23.
18. Wiggers T, Arends JW, Volovics A. Regression analysis of prognostic factors in colorectal cancer after curative resection. *Dis Colon Rectum* 1988;31:33–41.
19. Minsky BD, Mies C, Rich TA, Recht A. Lymphatic vessel invasion is an independent prognostic factor for survival in colorectal cancer. *Int J Radiat Oncol Biol Phys* 1989;17:311–8.
20. Connelly JH, Robey-Cafferty SS, Cleary KR. Mucinous carcinomas of the colon and rectum. An analysis of 62 stage B and C lesions. *Arch Pathol Lab Med* 1991;115:1022–5.
21. Green JB, Timmcke AE, Mitchell WT. Mucinous carcinoma—Just another colon cancer? *Dis Colon Rectum* 1993;36:49–54.