BACKGROUND: The treatment of rectal cancer has improved significantly over the last century. Advances in surgical and adjuvant therapy coupled with a better understanding of the natural history have allowed for acceptance of progressively diminished margins for distal neoplasms. In order to better define oncologically safe distal margins, we performed a meta-analysis of the existing world’s literature.

STUDY DESIGN: Studies were identified on Medline and ISI Web of Science using key words rectal cancer and margin. Studies were excluded if specific margins and local recurrence rates could not be extracted. All analyses were performed using Comprehensive Meta-Analysis Software (Biostat).

RESULTS: Twenty-one studies reported outcomes in relationship to distal margins. Seventeen studies, 4,885 patients, reported outcomes with margins of less than 1 cm. Analysis of all studies indicated a nonsignificant trend favoring greater margins. However, in order to understand distal margins in the context of current care standards, additional analyses were performed. Thirteen studies reported application of total mesorectal excision and/or radiation. There was no significant difference in local recurrence rates for margins less than 1 cm. In the 4 studies that reported neither total mesorectal excision nor radiation, a margin greater than 1 cm was favored. Increased recurrence rates and decreased survival were associated with positive final margins.

CONCLUSIONS: When total mesorectal excision is combined with radiotherapy, excellent local control can be expected with sphincter preservation for distal rectal cancers when margins are less than 1 cm, as long as final pathologic margins are negative. (J Am Coll Surg 2011;213:589–595. © 2011 by the American College of Surgeons)

The treatment of rectal cancer has advanced significantly over the last century. Before the 17th century, surgical therapy consisted primarily of diversion for obstruction.1 In the early 20th century, this disease was most often fatal and was treated via a perineal approach.2 Secondary to poor local control and data derived from autopsy studies, W Ernest Miles, in 1908, recommended a more radical operation to address zones of proximal, lateral, and distal spread.1,3 Soon after, abdominal perineal resection, or the Miles procedure, became the standard approach for all rectal cancers.1

Beginning in the 1930s, various pull-through procedures and hand sewn anastomoses were applied to upper rectal cancer.2 In 1948, Claude Dixon reported excellent results for 523 patients undergoing anterior resection for upper and middle rectal cancers.2,4,5 A progressive diminution of acceptable distal margins and an increase in function-preserving surgery ensued over the next several decades.5 The need for an abdominoperineal resection for all rectal cancers was abandoned in favor of a 5-cm distal margin as it became clear the zone of distal spread had been overestimated.4,6 The advent of modern circular stapling devices introduced by US Surgical Corporation in the late 1970s made continent-preserving procedures for distal rectal cancers more technically feasible.2,4,7 In addition to improved surgical instrumentation, there have been advances in surgical technique. Sphincter-preserving procedures such as intersphincteric dissection provide the ability to perform very low pelvis anastomosis.8-12 In this era, multiple series reported outcomes in relationship to distal margins (Table 1).13-18 Although the studies are somewhat inconsistent, a 2-cm distal margin became widely accepted.

Additionally, there has been a significant evolution and increased application of adjuvant therapy. Postoperative radiation therapy has been shown to improve local control and has decreased local recurrence from 25% to 16%, but not overall survival when compared with surgery alone.19 In 1985, the
Gastrointestinal Tumor Study Group reported improved local control and disease-free survival with postoperative chemoradiotherapy; recurrence rates were 55% for patients who underwent only surgery and 33% for those who also received chemoradiotherapy. Although these findings were not supported in a meta-analysis, studies of preoperative adjuvant chemoradiotherapy reported tumor downstaging with resultant increases of 3% to 20% in sphincter preservation. Total mesorectal excision (TME), as introduced by Bill Heald, allowed this surgery to be done with a low pelvic recurrence rate. Advances in surgical and adjuvant therapies were accompanied by reports of oncologically sound outcomes in regard to local recurrence rates, with margins of less than 1 to 2 cm (Table 1). As a result, some authors have stated that abdominoperineal resection should be reserved for patients in whom negative distal margins cannot otherwise be achieved. In order to better define oncologically safe distal margins in rectal cancer patients, we performed a meta-analysis of studies reporting distal resection margins and incidence of local recurrence.

### METHODS

#### Literature search

The PubMed and ISI Web of Knowledge databases were used to identify potential studies. Search terms included "rectal cancer and margins" and "rectal cancer and distal margins." A total of 996 articles were identified. Titles were reviewed and abstracts were individually analyzed if they potentially met inclusion criteria. A manual search was also conducted of the references in selected articles to obtain a more exhaustive list of relevant literature. No restrictions were made based on data type, year of publication, or patient age. The primary endpoint of this analysis was to define the association between distal margins and local recurrence rates. Studies were considered for inclusion if patients with rectal cancer underwent surgical resection, margins were noted, and local recurrence rates reported. Studies were excluded if individual case level margins or local recurrence rates could not be extracted, data regarding adjuvant therapy were not reported, if published in abstract form only, or if long-term follow-up information was not available. All studies were retrospective or prospective cohorts; no prospective randomized trials were found that addressed this endpoint. Articles were included only after review of the full manuscript by 2 authors and there was agreement on the quality of abstracted data (TLF and JB).

### Table 1. All Studies Identified Reporting Comparison of Greater and Lesser Distal Margins

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Study years</th>
<th>n</th>
<th>TME</th>
<th>XRT</th>
<th>0 cm margins</th>
<th>Outcomes: local recurrence</th>
<th>Median follow-up, mo</th>
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<tr>
<td>Kiran</td>
<td>2011</td>
<td>1991–2006</td>
<td>674</td>
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<td>Yes</td>
<td>Yes*</td>
<td>Equivalent</td>
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<td>Nash</td>
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<td>1991–2003</td>
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<td>Yes</td>
<td>Yes*</td>
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<td>Silberfien</td>
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<td>Leo</td>
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<td>1990–2004</td>
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<td>Yes</td>
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<td>Chiappa</td>
<td>2004</td>
<td>1994–2003</td>
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<td>Moore</td>
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<td>Andreola</td>
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<td>Yes</td>
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<td>Stockert</td>
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<td>No</td>
<td>Yes</td>
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<td>Bozzetti</td>
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<td>Vernava</td>
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<td>Secco</td>
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<td>1975–1981</td>
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<td>No</td>
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<td>1962–1982</td>
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<td>No</td>
<td>Yes</td>
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<td>Wolmark</td>
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<td>1977–2</td>
<td>181</td>
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<td>Yes</td>
<td>No</td>
<td>Increase</td>
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<tr>
<td>Heimann</td>
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<td>1973–1982</td>
<td>202</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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<td>Equivalent</td>
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<td>Pollett</td>
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<td>1963–1974</td>
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<td>Williams</td>
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<td>79</td>
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</table>

1 Distal margin cutoff was 0.8 cm.
2 TME, total mesorectal excision; XRT, radiotherapy.
associated with margin length. Using this model, 21 articles conforming to the criteria were identified and included in this meta-analysis.

**Data evaluation**

Articles were independently reviewed by study authors from the Division of Surgical Oncology and the Department of Biostatistics at East Carolina University. The primary study endpoint was local recurrence and distal margins. Additional extracted variables included year of publication, span of years in which the study was conducted, number of patients, TME documented, adjuvant radiotherapy, follow-up, and overall survival. Data extraction was independently performed by authors TLF and JB.

**Statistical analysis**

All analyses were performed using Comprehensive Meta-Analysis software (Biostat). Given the changes in study populations over time and the potential differences in participants (environment, lifestyle, etc.), our meta-analysis used a random weighting scheme, as described by Borenstein and colleagues. Values were aggregated across studies to determine overall impact and to calculate p values. Four analyses were performed using differing selection criteria in order to better define the impact of therapeutic variation secondary to TME and adjuvant therapy. First, we examined an overall model including all studies reporting margins of less than 1 cm, regardless of surgical technique or adjuvant therapy. We also analyzed the effects of TME and adjuvant radiotherapy independently. Finally, secondary to a significant overlap in the application of optimal surgical and adjuvant therapy, an analysis was performed examining the effect of TME and/or adjuvant radiotherapy.

**RESULTS**

**Studies**

Twenty-one studies were identified that reported greater or smaller margins and incidents of local recurrence (Table 1). The intention of this meta-analysis was to define the oncologic adequacy of smaller margins. To this end, we examined only the 17 studies reporting margins of less than 1 cm. We chose to include 2 studies whose distal margins were bound by 0.8 cm instead of 1 cm (under the assumption that relatively few patients would enter into that study with distal margins greater than 0.8 but less than 1 cm). Overall, in the 21 studies, there were 5,524 patients. After excluding 4 studies that did not report margins less than 1 cm, there were 4,885 patients (Table 1).

**Seventeen studies reporting margins less than 1 cm**

Seventeen studies reported outcomes with margins of less than 1 cm (Table 1). There was insufficient evidence to conclude superiority of margins greater than 1 cm, with a meta p value of 0.075 (Fig. 1). There was, however, a non-significant trend favoring greater than 1-cm margins, with a meta-odds ratio of 1.338.

**Stratified analysis with TME and/or adjuvant radiotherapy**

Significant overlap exists between adjuvant radiotherapy and TME (Table 1). Thirteen of 17 studies reported the use of TME and/or radiation therapy. When neither TME nor radiotherapy were aspects of the treatment regimen, the data clearly supported margins greater than 1 cm, with a meta-odds ratio of 2.528 and a meta p value of 0.005 (Fig. 2). When TME and/or radiotherapy were reported, the distal margins had no significant impact, with a meta-odds ratio of 1.129, and a meta p value of 0.456 (Fig. 2). Similar analyses were performed stratifying separately for TME and radiotherapy, with results almost identical to those reported in Figure 2. Because these data do not contribute significantly to the conclusions, Forest plots are not presented. Given that only a handful of the reports used TME or radiotherapy exclusively, we were not able to discern individual contributions to outcomes.

**DISCUSSION**

Over the last century, treatment of patients with rectal carcinoma has improved significantly. In the early 20th century, secondary to poor outcomes with surgical therapy and postmortem evaluation of patients, abdominoperineal resection was adopted and became the standard treatment of rectal cancer. Subsequent advances in knowledge, surgical technique, and adjuvant therapy have resulted in an increased ability to provide sphincter-sparing surgery for low rectal cancer with progressively smaller distal margins. In this analysis we found that sphincter preservation can safely be considered with less than a 1-cm margin.

Multiple prospective and retrospective studies have evaluated distal margins for low rectal cancers, and variable outcomes have been reported (Table 1). Dogmatic adherence to abdominal perineal resection for upper rectal cancers gave way to acceptance of a 5-cm distal margin. Investigators from the Leeds Clinic published a reprisal of the 5-cm rule for distal rectal carcinoma in 1983. This study reported outcomes in 79 patients with distal rectal cancers, 48 of whom had distal margins less than 5 cm. There was no increase in recurrence or mortality, and pathologic intramural spread rarely ex-
ceeded 1 cm. Over the next decade, multiple publications reported outcomes for lesser margins. These consistently demonstrated no detriment to margins greater than 2 cm, but the data were inconsistent for smaller distances.13-18,38-40 Based largely on these data, a 2-cm distal margin became the accepted standard.

In contrast to older reports, contemporary series report no detrimental oncologic outcomes associated with smaller, but negative, distal margins.7,26,27,29,30,32-34,41-44 TME and adjuvant radiation therapy decreased local recurrence rates and allowed for an increase in sphincter preservation. In 1992, surgeons from Basingstoke Hospital reported the effects of TME on rectal cancer recurrence with less than 1-cm margins.18 In this series, 152 patients underwent a curative TME without adjuvant radiotherapy and were stratified by margins greater than 1 cm or less than 1 cm (110 patients vs 42 patients, respectively). The outcomes were equivalent, and the authors concluded that a margin less than 1 cm was adequate in the setting of proper surgery.

Treatments in most contemporary series combine both optimal surgery and adjuvant radiotherapy. Most of these studies reported equivalence for patients with less than 1-cm distal margins (Table 1).7,26,27,29,30,32-34,40-43 Outcomes were similar for different regimens including preoperative chemoradiotherapy, preoperative short-course radiotherapy, and postoperative chemoradiotherapy. Two small series reported local recurrence rates for patients with low rectal cancer treated with preoperative chemoradiotherapy; no difference was noted for margins of greater or less than 1 cm.32,33 In a much larger series from Seoul, 914 patients were selectively treated with preoperative chemoradiotherapy for T4 or stage III tumors followed by TME. Patients with unanticipated advanced disease were treated with postoperative chemoradiotherapy.26 Equivalent local and anastomotic recurrence rates were noted in 167 patients with margins of less than 1 cm when compared with those with larger margins. Two more recent large series with similar treatment regimens corroborate these findings.43,44 Similar results have been noted with short-course preoperative radiotherapy.31

TME with postoperative chemoradiotherapy is also associated with an ability to safely minimize distal margins. Andreola and colleagues34 reported an experience with 87 stage III patients undergoing mesorectal clearance with postoperative adjuvant radiotherapy. There were no differences in local recurrence rates or overall survival for patients

Figure 1. Meta-analysis Forest Plot for all studies reporting margins of greater or less than 1 cm.
with margins less than 1 cm. Other investigators have confirmed this finding.30,34

This meta-analysis compiled 21 studies spanning more than 3 decades reporting local recurrence and other outcomes for patients with greater or lesser margins. Within this time frame, both TME and adjuvant radiotherapy became standard of care. To best define the minimal acceptable distal margin, we excluded studies that did not report margins of less than 1 cm. Seventeen studies were included in the final analysis. None of these were prospective randomized trials specifically addressing distal margins (Fig. 1). When taken in toto, there was no statistically significant deterrent for lesser margin distance, but a trend did favor a greater margin.

Secondary to significant disparity in outcomes between trials, subanalyses were performed in the context of current care standards. Given the significant overlap between TME and adjuvant radiotherapy, we analyzed all studies that reported use of either technique (Fig. 2). We found no significant deterrent to less than a 1-cm distal margin. In studies that did not report either technique, there was a profound disadvantage to the lesser margin. Given the concurrent evolution of both surgical and adjuvant therapies, it is impossible to discern the exact contribution of individual modalities. Indeed, in many studies included in this analysis, there was selective use of radiotherapy in high risk patients (generally T3/T4 and node positive).26,29,30,34,41-44

Positive distal margins have a profoundly negative effect for patients with rectal cancer, even with optimal surgical technique and adjuvant therapy. Recurrence rates as high 60% have been reported in patients with a positive distal margin who had been treated with TME and adjuvant radiotherapy.34 Two trials included in this meta-analysis addressed the implications of positive distal pathologic margins (Table 1). In these 2 studies, significantly elevated hazard ratios between positive and negative distal margins were noted.26,30 In the largest series, Kim and associates26 reported outcomes for 7 of 915 patients with negative intraoperative frozen sections but positive final pathology. The authors noted that this finding was associated with a 40% percent local recurrence rate and was an independent predictor of recurrence on multivariate analysis, with a hazard ratio of 16.8 (95% CI 4.8 to 59). Similarly, in a second series of 203 patients undergoing TME and postoperative radiotherapy, 12% of patients had positive final pathologic margins; 6 of these patients refused abdominal peritoneal resection.30 The local recurrence rate in this group was 30%, a decreased 5-year survival was noted, and the hazard ratio was 2.35 (95% CI 1.08 to 5.11). Based on such data, some authors have concluded that the only indication for abdominoperineal resection is the inability to obtain negative distal or radial margins.35,36

The study reported here has several limitations. First and foremost, this is a meta-analysis, not a prospective random-
ized trial, and has inherent limitations secondary to comparisons across trials and in different patient populations. TME and current adjuvant therapy standards emerged during the same era and it is impossible to determine individual therapeutic contributions. Additionally, there were variations across studies in the definition of local failure and distal margins (gross margins and/or final pathologic margins). Because we don’t have access to case level data, there may be unreported confounding variables. Finally, because follow-up ranged from 37 to 81 months, we were limited in conclusions that can be made for longer-term outcomes (Table 1).

**CONCLUSIONS**

These data, taken in context with current literature, indicate that excellent local control can be expected with sphincter-preserving surgery for distal rectal cancers having resection margins of less than 1 cm when TME is combined with preoperative chemoradiotherapy, preoperative short-course radiotherapy, or postoperative chemoradiotherapy. There are no clear data to indicate a deterrent to any course radiotherapy, or postoperative chemoradiotherapy. There are no clear data to indicate a determent to any with preoperative chemoradiotherapy, preoperative short-term results of a randomized trial comparing preoperative short-course resection for rectal cancer: Preliminary results–EORTC 22921. J Clin Oncol 2005:23:5620–5627.


REFERENCES


