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Local Excision for ypT2 Rectal Cancer—Much Ado About Something

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Abstract
Background The role of local excision for pT2 distal rectal cancer has been challenged because of the observation of high rates of lymph node metastases and local failure. However, neoadjuvant chemoradiation therapy (CRT) has led to increased local disease control and significant tumor downstaging, possibly decreasing rates of lymph node metastases. In this setting, a possible role for local excision of ypT2 has been suggested.
Methods A total of 401 patients with distal rectal cancer underwent neoadjuvant CRT. Tumor response assessment was performed after at least 8 weeks from CRT completion. One hundred and twelve patients with complete clinical response were not immediately operated on and were excluded from the study, and 289 patients with incomplete clinical response were managed by radical surgery. Patients with final pathological stage ypT2 were analyzed to determine the risk of unfavorable pathological features that could represent unacceptable risk for local failure after local excision.
Results Eighty-eight (30%) patients had ypT2 rectal cancer. Final ypT status was not associated with pretreatment radiological staging (p=0.62). ypT status was significantly associated with the risk of lymph node metastases, risk of perineural and vascular invasion, and recurrence (p=0.001). Lymph node metastases were present in 19% of patients with ypT2 rectal cancer. The risk of lymph node metastases in ypT2 was associated with the presence of perineural invasion (47% vs 4%; p=<0.001), vascular invasion (59% vs 6%; p<0.001), and decreased mean interval CRT surgery (12 vs 18 weeks; p<0.001), but not with mean tumor size (3.2 vs 3.1 cm; p=0.8). Disease-free and overall survival rates were significantly better for patients with ypT2N0 (p=0.02 and 0.006, respectively). Fifty-five (63%) patients with ypT2 had at least one unfavorable pathological feature for local excision (lymph node metastases, vascular or perineural invasion, mucinous type or tumor size >3 cm).
Conclusion Lymph node metastases were present in 19% of patients with ypT2 and were significantly associated with poor overall and disease-free survival rates. The risk of lymph node metastases could not be predicted by radiological staging or tumor size. Radical surgery should be considered the standard treatment option for ypT2 rectal cancer after CRT.

Keywords Rectal cancer · Neoadjuvant therapy · Staging · Risk · Recurrence · Outcome

Introduction

Optimal treatment of early rectal cancer remains controversial. Although radical surgery alone leads to excellent oncological outcomes, it is associated with significant

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morbidity rates including early postoperative complications, urinary or sexual dysfunction, and requirement for temporary or definitive stomas.[1–3] For these reasons, alternative management options have been studied for the management of early rectal cancer.[4]

Local transanal excision of rectal cancer was initially considered an option for these patients. As the risk of local recurrence has a direct association with the risk of lymph node metastases in these patients, ideal candidates for local excision as a radical treatment option included patients with early rectal cancer and favorable pathological features including depth of tumor penetration, tumor differentiation, absence of vascular invasion, tumor size, and absence of ulceration.[4] However, the risk of lymph node metastases in these patients may reach rates over 13% even in pT1 rectal cancer.[5] Moreover, long-term results showed disappointing local recurrence rates of 15–30% in these patients.[6]

Introduction of neoadjuvant chemoradiation therapy (CRT) followed by radical surgery for the management of advanced rectal cancer has resulted in significant advantages in terms of toxicity, sphincter preservation, local disease control, and tumor downstaging.[7] In fact, tumor downstaging not only was observed for the primary tumor, but also for lymph node metastases, reflected by the significant decrease of stage III among these patients.[7–9] The observation of significant tumor regression in patients undergoing neoadjuvant chemoradiation has led to the utilization of alternative treatment options in patients with tumors downstaged to stage yI or even stage y0.[10] In this setting, patients with early rectal cancers (ypT1 and ypT2) after neoadjuvant CRT would be candidates for local excision, as the risk for lymph node metastases would be significantly reduced by the possible sterilization effect of CRT. Also, these tumors frequently exhibit significant downsizing after CRT, therefore facilitating the excision of a margin-negative specimen through a transanal approach. Following this rationale, a multicenter trial is now open for accrual in the United States including patients for neoadjuvant CRT followed by local excision alone in patients with ypT0-2.[11]

For this reason, we decided to review a large series of patients with distal rectal cancer managed by neoadjuvant CRT followed by radical surgery with ypT2 to determine long-term oncological results and pathological features that could possibly predict the results of local excision alone for these patients.

Patients and Methods

Four hundred and one patients with distal rectal adenocarcinoma and no radiological signs of distant metastatic disease underwent neoadjuvant CRT as described elsewhere.[12] Tumor response assessment was performed at least 8 weeks from CRT completion and included complete physical examination, DRE, rigid proctoscopy, CEA levels, abdomino/pelvic CT scans, and chest radiographs. Patients with any suspicious scar or lesion were locally excised for pathological examination. Patients with no clinical residual disease or those with negative pathological results of any excised scars were considered complete responders and were not immediately operated on.[13] Those patients who sustained complete clinical response for at least 12 months were considered Clinical Stage 0 and were excluded from this study and are reported elsewhere.[14]

Patients with incomplete clinical response detected at initial tumor response assessment or those with early tumor regrowth (within 12 months) after initial suspected complete clinical response were referred to surgery.

Radical surgery included abdominal-perineal resection, low anterior resections with coloanal or low colorectal anastomosis. All patients underwent TME and high arterial ligation of the inferior mesenteric artery (IMA). After specimen removal, 2-cm macroscopic-free distal margins were considered adequate. Final pathological examination was performed by two GI-dedicated collaborating pathologists. Patients were staged according to AJCC recommendations.[15]

Patients included in the statistical analysis were those with pathological evidence of residual cancer invading muscularis propriae after neoadjuvant chemoradiation (ypT2), irrespective of initial disease staging.

Follow-up was performed by two colorectal surgeons every 3 months for the first 2 years, every 6 months until the fourth year and yearly thereafter. Patients with pathological stage III (ypTanyN1-3M0) were referred to a medical oncologist for consideration of adjuvant chemotherapy.

Recurrences were classified into local (endorectal or pelvic), systemic or combined (local and systemic).

Statistical analysis was performed using Chi-square and Student's t tests for categorical and numeral variables between groups. Logistic and Cox's regression models were used multivariate risk factor and survival analysis. Survival analysis was performed using Kaplan–Meier curves and log-rank test. Significant differences were considered for p values <0.05.

Simulation of Recurrence After Local Excision ypT2

Considering that local recurrence rates after local excision for early rectal cancer parallels the incidence of lymph node metastases of these tumors, we simulated the expected additional local recurrence rates in the present series of ypT2 patients as if they were managed by local excision instead of radical surgery after neoadjuvant CRT. All ypT2 patients with positive lymph node metastases who did not

develop local recurrences in our series would be at a high risk for developing recurrence had local excision been performed on them instead of radical resection. We simulated disease-free survival (DFS) where only patients with N+ disease would have developed relapse had local excision been performed on them instead of radical resection. The recurrence time patterns for the current series (including N+ and N0 patients) was used to estimate survival. This simulation was performed to estimate the impact of not performing radical surgery in this subset of patients.

Results

Of the 401 patients undergoing neoadjuvant CRT, 112 were considered to have complete clinical response; they were not immediately operated on and were excluded from the study. A total of 289 patients underwent radical surgery after CRT and constitute the study population. Overall pretreatment characteristics are summarized in Table 1 and posttreatment characteristics are summarized in Table 2.

Overall recurrence rate was 33% including endorectal recurrences in 5%, pelvic recurrences in 8%, and systemic recurrences in 20%. There were 17% and 13% of overall and cancer-related deaths, respectively.

Table 1 Overall Pretreatment Characteristics of Patients with Rectal Cancer Treated with Neoadjuvant CRT Followed by Radical Surgery

Characteristics	Values
n	289
Age	
Mean years	58±13
Sex	
Female	116(40%)
Male	173(60%)
Pretreatment characteristics	
Mean tumor size	4.1±1.2 cm
Mean distance from verge	3.9±1.7 cm
Mean CEA	13.5±36.1 ng/dl
Pretreatment staging[a]	
T	
2	21(11%)
3	168(85%)
4	9(4%)
N	
0	145 (73%)
+	53(27%)
Stage	
I	20 (10%)
II	125 (63%)
III	53 (27%)
Mean CRT-surgery interval	18±10 weeks
Surgery	
APR	156 (54%)
SSO	133 (46%)

[a] Pretreatment staging available for 198 patients

Table 2 Overall Pathological Characteristics of Patients with Rectal Cancer Treated with Neoadjuvant CRT Followed by Radical Surgery

Characteristics	Values
Tumor characteristics	
Mean tumor size	3.4±1.2 cm
Recovered nodes	
Mean	9.9±9.0
AJCC/UICC Staging	
ypT	
0	24 (8%)
1	18 (6%)
2	88 (31%)
3	145 (50%)
4	14 (5%)
ypN	
N0	213 (74%)
N+	76 (26%)
Final stage	
yp0	24 (8%)
ypI	87 (30%)
ypII	102 (35%)
ypIII	76 (27%)

ypT2

A total of 88 patients were found to have ypT2 tumors after surgery. Of these patients, 51 (58%) underwent an abdominoperineal resection (APR) and 32 (42%) a low anterior resection (LAR). Mean total number of recovered lymph nodes (LN)/specimens was 10.7±12, mean tumor size was 3.2±1.5 cm, and mean distal margin was 2.6±1.8 cm. Accurate tumor size was available for 76 of these patients.

Of the 88 patients with ypT2 lesions at final pathology, 17 (19%) had positive lymph nodes, 15 (18%) had well-differentiated tumors, 11 (12%) had perineural invasion, 14 (16%) had vascular invasion, and eight (9%) were mucinous-type tumors. Overall, 55 (63%) patients with ypT2 had at least one unfavorable pathological feature (lymph node metastases, vascular or perineural invasion, mucinous type or tumor size >3 cm) (Table 3).

Even in patients with small ypT2 lesions (<3 cm in diameter), there was no decreased risk of unfavorable pathologic features including lymph node metastases (23% vs. 19%; $p=0.6$), perineural invasion (11% vs. 13%; $p=0.8$), vascular invasion (21% vs. 13%; $p=0.3$) or mucinous component (9% vs. 6%; $p=0.6$) (Table 4).

Overall, there was a significant association between the presence of lymph node metastases and perineural invasion

Table 3 Surgical and Pathological Features of Patients with ypT2 Rectal Tumors

Characteristics ypT2 (n=88)	Values
Type of surgery	
APR	51 (58%)
SSO	32 (42%)
Mean number LN/specimen	10.7±12
Mean tumor size (cm)	3.2±1.5
Lymph node metastases (ypN+)	17 (19%)
Well differentiated	15 (18%)
Perineural invasion	11 (12%)
Vascular invasion	14 (16%)
Mucinous type	8 (9%)
At least one unfavorable pathological feature	55 (63%)

(47% vs. 4%; p<0.001), vascular invasion (59% vs. 6%; p< 0.001) and shorter interval between CRT and surgery (18 vs. 12 weeks; p<0.001) (Table 5). Mean follow-up period was 57±49 months.

Recurrences and Survival

Overall, there were 21 recurrences (24%) among patients with ypT2, including eight (9%) local recurrences (two endorectal and six pelvic) and 13 systemic recurrences (15%). Among these patients, four were amenable to curative treatment, 10 died of disease-progression, and seven are alive with evidence of disease. Only nine (43%) of the patients who developed recurrence had positive LN, and of these only three developed local recurrences.

At univariate analysis, significant predictive factors for overall recurrence included presence of lymph node metastases (ypN+) and perineural invasion (p=0.002 and 0.01, respectively). After multivariate analysis, only the presence of lymph node metastases remained a significant predictor of recurrence (p=0.003; OR=5.5, 95% CI 1.7–17.2).

Interestingly, the presence of perineural invasion was the only significant predictive factor for local recurrence at univariate analysis (36% vs. 5%; p=0.001).

Five-year overall and disease-free survival was 86% and 66%, respectively. Patients with N+ disease had significantly worse OS and DFS rates (OS: 89% vs. 49%; p=0.02 and DFS: 75% vs 30%; p=0.0006; Figs. 1 and 2) At univariate analysis, the presence of lymph node metastases was the only significant predictor of poor outcome among patients with ypT2 tumors (p=0.003).

After simulation in which patients with ypT2N+ developed recurrences, as it would be expected after local excision instead of radical surgery, 5-year local recurrence rates were significantly worse than in patients managed by radical surgery after neoadjuvant CRT (5-year LR 33% vs 14%; p=0.009; Fig. 3).

Table 4 Surgical and Pathological Features in ypT2 Rectal Cancer According to Final Tumor Size

	Size < 3 cm	Size > 3 cm	p
n	44 (58%)	32 (42%)	
ypN			
ypN0	34 (77%)	26 (81%)	
ypN+	10 (23%)	6 (19%)	0.6
Differentiation			
Moderate	37 (84%)	24 (77%)	
Well	7 (16%)	7 (23%)	0.4
Invasion			
Lympho-Vascular	5(11%)	4(13%)	0.8
Perineural	9(21%)	4(13%)	0.3
Mucinous type	4(9%)	2(6%)	0.6

Accurate tumor size was available for 76 of the 88 ypT2 patients

Table 5 Association Between Lymph Node Metastases and Other Clinico-pathological Features in ypT2 Rectal Tumors

	ypN+	ypN0	p
N	17 (19%)	71(81%)	
Mean age (years)	58.4±17.0	5.7±13.7	0.77
Gender			
Male	7 (41%)	47 (66%)	0.051
Female	10 (59%)	24 (34%)	
Prereatment characteristics			
Tumor size(mm)	40.6±12.7	43.2±12.2	0.49
Distance from anal verge(cm)	3.2±1.2	3.6±2.0	0.41
Clinico-Radiological Stage			
I	3 (21%)	3 (6%)	0.08
II	7 (50%)	39 (78%)	
III	4 (29%)	8 (16%)	
Type of Surgery			
APR	11 (65%)	40 (56%)	0.53
SSO	6 (35%)	31 (44%)	
CRT-Surgery Interval (weeks)	12.2±4.3	18.4±12.4	<0.001
Mean tumor size (cm)	31.8±14.9	32.5±15.2	0.87
Differentiation			
Well	14 (83%)	55 (82%)	0.98
Moderate	3 (18%)	12 (18%)	
Invasion			
Perineural	8 (47%)	3 (4%)	<0.001
Vascular	10 (59%)	4 (6%)	<0.001
Mucinous type	2 (12%)	6 (9%)	0.66

Discussion

Radical surgery has resulted in excellent oncological outcomes of patients with early rectal cancer (stage I disease).[1,16–18] However, these results were not at low cost. In fact, overall morbidity and mortality rates are significant after radical

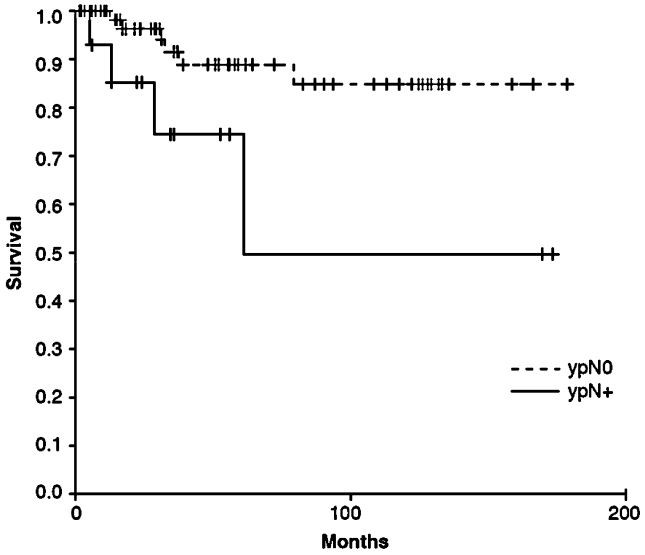

Figure 1 Overall survival according to ypN status in patients with ypT2 rectal tumors. Five-year overall survival was 89% for ypN0 and 49% for ypN+ patients, which was significantly different (p=0.02).

surgery for rectal cancer including total mesorectal excision varying from 7% to 68% and 0% to 6%, respectively.[4,7,19] Moreover, these operations are frequently followed by readmissions to the hospital because of postoperative complications, significant rates of permanent and temporary stomas, and sexual or urinary dysfunction.[3,20,21] Finally, adequate total mesorectal excision (TME) demands specific training, and incomplete rates of TME may reach up to 40% of operations performed and positive circumferential margins in over 10% of patients, specially in distally located tumors.[22,23]

In this setting, an alternative radical treatment strategy was warranted. Transanal full-thickness local excision with

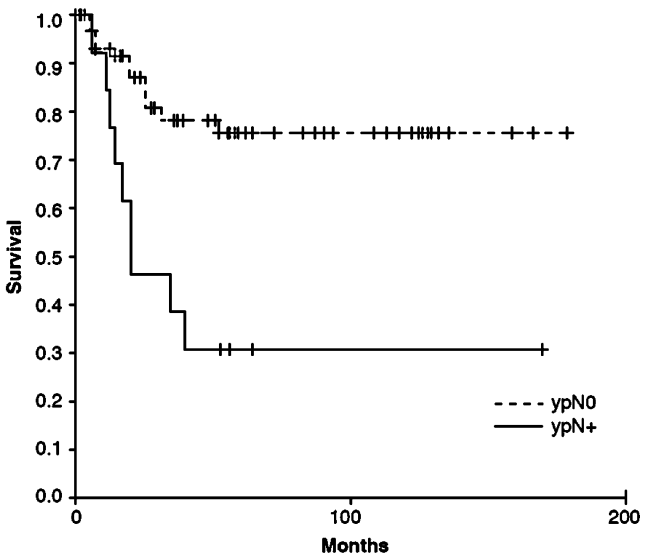

Figure 2 Disease-free survival according to ypN status in patients with ypT2 rectal tumors. Five-year disease-free survival was 75% for ypN0 and 30% for ypN+ patients, which was significantly different (p=0.006).

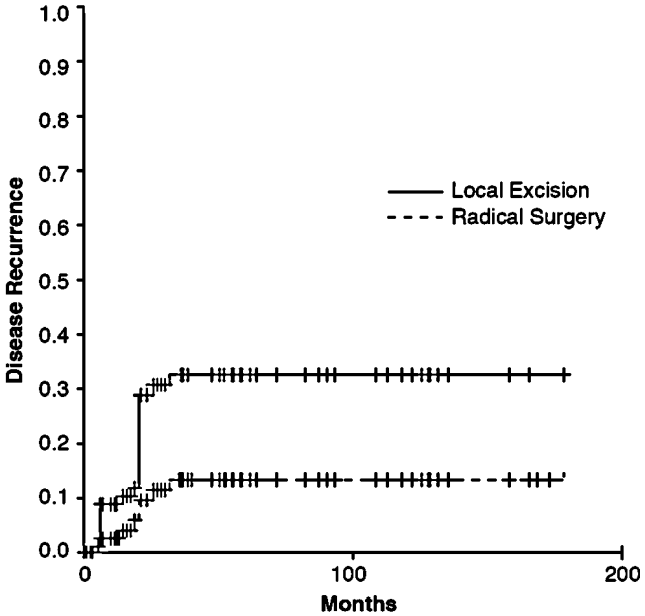

Figure 3 Local recurrence rates simulation comparing patients with ypT2 after radical surgery to local excision (LE) alone, considering patients with ypN+ would have recurred if LE was performed instead of radical surgery. LE estimated disease-free survival (DFS [local relapse]) were significantly worse to those observed after radical surgery (86% vs 67%; p=0.009).

free margins was initially considered an ideal treatment option for these patients with early rectal cancer (pT1-2) as a result of its low associated morbidity, no requirement for stomas, absent mortality, excellent functional and oncological outcomes.[4] However, as there is neither lymph node nor mesorectal excision with this approach, selection of patients included identification of favorable features that could predict minimal risk for lymph node metastases in these patients. In a large retrospective study of patients with pT1 colorectal cancer, the overall risk for lymph node metastases was 13%. After multivariate analysis, this same study identified depth of submucosal invasion and presence of lymphovascular invasion as significant predictors of lymph node metastases.[5] Interestingly, in their series, distal rectal location, which is considered the ideal location for local excision, was also a significant risk factor for lymph node metastases.[5] In a similar study of patients with pT1 colorectal cancer, predictive pathological features for lymph node metastases, observed in 11% of this series, included poor tumor differentiation, lymphovascular invasion, peritumoral inflammation and budding at the invasive front of the tumor.[24]

Therefore, local excision was considered as an alternative radical treatment option by many in selected patients with well-differentiated pT1-2, radiological evidence of N0 and M0, accessible (low) and small tumors (<3–4 cm).[4] However, results were disappointing. In a review of 22 studies including more than 900 patients after local excision

alone for rectal cancer, local relapse for pT2 was 25%, ranging from 0% to 50%.[25] Besides differences in patient selection, other variables such as surgical technique, assessment of resection adequacy, and salvage procedures may have contributed to the wide range of results. In another study of patients with pT2 undergoing local excision alone, it was shown that 37% had local relapse after 54 months of follow-up.[26] Moreover, these authors compared patients with pT2 after LE alone to patients with pT2 after radical surgery in a retrospective study and demonstrated significantly higher overall and local recurrence rates and decreased disease-free survival associated with LE. Apparently, these differences remained significant even after exclusion of patients with unfavorable pathology.[17]

In this setting, there was room for improvement, and radiation therapy alone or combined with chemotherapy was considered either pre- or postoperatively.[4] Although adjuvant CRT after LE has resulted in lower local and overall recurrence rates in small retrospective studies, the neoadjuvant approach seems to be better tolerated, less toxic, and more effective.[7, 27] In fact, neoadjuvant CRT may lead to significant tumor downstaging and downsizing. These advantages may not only facilitate surgical resection caused by decrease in tumor size, but also decrease the risk of lymph node metastases and micrometastases.[7–9,28]

In a retrospective series of patients undergoing neoadjuvant CRT followed by radical surgery after 6–8 weeks, the rate of lymph node metastases was significantly affected by ypT stage. The rate of LN metastases in patients with ypT2 was 16.9% in this series of patients.[29] In another reported series of patients with distal rectal cancer after CRT and radical surgery, ypT2 had 21% risk of lymph node metastases.[30] In our study, ypT stage was also a significant predictor of lymph node metastases, and ypT2 had a 19% of positive lymph nodes. Although there seems to be less number of patients with stage III disease after neoadjuvant CRT, the rates of lymph node metastases in ypT2 seem considerably high, especially when considering local excision. One argument could be raised, stating that these metastatic nodes would be clinically irrelevant after CRT in terms of recurrence and survival. In a previous report, we found final pathological stage to remain a significant prognostic factor after neoadjuvant CRT.[31] In fact, in an interesting retrospective study of patients after CRT and radical surgery, final pathological features including final pathological disease stage, presence of lymph node metastases and lymphovascular invasion were all shown to be significant predictors of disease-free and overall survival.[30] Therefore, these so-called unfavorable pathological features seem to be clinically relevant even after CRT and probably should be considered before embarking on alternative treatment strategies for distal rectal cancer, a location that by itself constitutes a significant predictor of disease recurrence.[5] In our study, the rate of positive lymph nodes among patients with ypT2 was 19%, lymphovascular invasion was 15%, perineural invasion was 12% and mucinous type tumors were observed in 10%. In addition, the presence of at least one unfavorable pathological feature was found in over 60% of these patients. The presence of lymph node metastases was a significant predictor for overall recurrence, whereas perineural invasion was a significant predictor of local recurrence, further emphasizing the clinical relevance of these unfavorable features. Interestingly, 53% of patients with ypN+ disease developed recurrences. Therefore, there would a potential significant increase in overall and local recurrence rates had these (metastatic) lymph nodes not been removed. Considering lymph node metastases was not a significant predictor of local failure in our series, these results suggest that radical resection in the setting of N+ disease may have a significant role in optimizing results, especially in terms of local disease control.

Although there was a significant downsizing of tumors after CRT (4.2 vs 3.2 cm), the risk of lymph node metastases remained unchanged in patients with small tumors (<3 cm). In fact, small tumors (<3 cm) had similar risks of lymph node metastases, perineural invasion, lymphovascular invasion, and mucinous type tumors when compared to larger lesions (>3 cm). Small tumors were significantly associated with sphincter-preserving operations and there was no difference in overall or disease-free survival. Although size has been considered a selection criterion for local excision, our data support that this feature may be related only to technical issues. Larger lesions may have more difficulty undergoing complete negative-margin resection and therefore are associated with increased risk of recurrence, rather than a higher risk of harboring lymph node metastases, lymphovascular or perineural invasion, and mucinous type tumors.

In fact, the addition of neoadjuvant CRT to the management of rectal cancer has raised significant issues in terms of the choice of type of operation, benefit of additional adjuvant therapy, and the usefulness of final pathological features in prognosis estimation. Randomized controlled trials have demonstrated a benefit in sphincter preservation favoring the neoadjuvant therapy group.[7,32] This is related to the observation that tumors that exhibited downsizing and downstaging were more amenable to sphincter-preserving operations and therefore indicates that surgeons decided on the type of operation after neoadjuvant therapy. The interval between CRT and surgery may actually further impact the rate of sphincter preservation.[32] Also, it has been shown that the final pathological features, even after neoadjuvant CRT, remain significant prognostic factors.[30,31] On the other hand, final pathology staging of ypT2 may include tumors with different biological behav-

iors as reflected by their initial disease staging. ypT2 that was already a cT2 showing no response to CRT may be indistinguishable from a cT4 that showed significant response to CRT. Still, in our current series pretreatment staging (including cT and cN) was not a predictor of recurrence or survival, albeit pretreatment staging was not available for all patients. In the subset of patients with complete clinical response managed by non-operative management reported elsewhere, there were 13% of patients with initial cT2N0 disease.[14] Again, pretreatment staging was not a predictor of recurrence among this subset of patients. Therefore, in a setting where accurate staging for rectal cancer is lacking, especially after neoadjuvant CRT, it seems reasonable to make management decisions, such as type of surgery to be performed and prognostic information, based on posttreatment (CRT) status.

The ACOSOG 6041 is based on uT2N0 rectal cancers undergoing neoadjuvant CRT followed by local excision. In this study, patients with final pathological ypT2 will be considered for observation without immediate radical surgery.[11] In fact, this subpopulation of the study will represent a subset of patients with no downstaging after CRT and therefore represent a different and rather worse (in terms of biological behavior) population when compared to our study.

Reviewing the results of local excision after neoadjuvant CRT in small retrospective series, reported recurrence rates may reach up to 25% and may closely relate to observed rates of lymph node metastases in these patients.[4,33] Interestingly, salvage surgery for recurrent rectal cancer after local excision seems to be associated with more advanced disease than the original primary and may not provide the same chance for cure as a radical resection performed as the initial treatment.[18,34] On the other hand, immediate radical surgery (not salvage radical surgery) after local excision for selected patients did not compromise outcome, especially when performed within 30 days.[18,35]

In our study, neoadjuvant CRT and radical surgery for ypT2 rectal cancer resulted in a 5-year overall recurrence rate of 34% and local recurrence rate of 14%. However, considering that this series of patients would have been treated by local excision for ypT2, additional recurrences could be expected for those patients who did not recur after radical surgery, but would have recurred as a result of positive lymph nodes left behind. In this hypothetical setting, local recurrence rates at 5-year follow-up would have reached an unacceptable rate of 33%, instead of 14%, after radical surgery.

In conclusion, ypT2 tumors after neoadjuvant CRT and radical surgery exhibit considerably high rates of lymph node metastases, lymphovascular invasion, perineural invasion, and mucinous type tumors. These pathological findings are considered unfavorable pathological features and were not associated with tumor size. At least one unfavorable pathological feature is present in over 60% of the patients. The presence of lymph node metastases and perineural invasion are clinically relevant features in predicting overall and local recurrence even after radical resection and would certainly play a role in recurrence after local excision. An additional recurrence rate would be expected after local excision as a result of leaving behind a significant proportion of patients with positive lymph node metastases. This expected increase in local failure after local excision of ypT2 might be considered unacceptable in a setting where salvage resection has been demonstrated to be associated with worse results than would be radical surgery as the initial treatment. In the setting where residual rectal cancer after neoadjuvant CRT leads to a ypT2 lesion, radical surgery should be strongly recommended and local excision regarded as a diagnostic, staging, or palliative procedure.

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DISCUSSION

Robert W. Beart, Jr., M.D. (Los Angeles, CA): We appreciate the opportunity to review this manuscript and I appreciated personally the opportunity to see it ahead of time. Your group has championed efforts nationally and internationally to tailor the extent of treatment to the extent of the disease. You are bringing your work repetitively to this forum for review, which we all appreciate at the SSAT.

The literature in this area is confusing. You confirm data that suggest that substantial downstaging is associated with improved survival and that in fact patients tend to behave as their pathologic stage after surgery rather than their clinical stage before surgery. But there's equally impressive data that suggest in large retrospective pathologic reviews that even a complete response to neoadjuvant therapy is not associated with a change in the incidence or patterns of recurrence. So I think at this stage this is a very confusing area, and I think your effort to shed some light on the issue is important.

I had a little trouble with the manuscript in that you focus on survival, but I think the real issue here is local control, and I am not sure that a radical operation will necessarily improve or change the incidence of liver metastases. I understand lymph node positivity is associated with long-term survival. In your manuscript, lymph node positivity was not associated with local occurrence, and so I think local control should be the focus.

I have just a few questions. First of all, you noticed a significant difference in the patients who had delayed surgery, out to 18 weeks, I believe, and I wondered if that long delay had an impact and if that is something to which we should be attentive.

Can you tell us what happened to the eight local recurrences? Were they controlled, were they manageable?

What about ongoing chemotherapy? You used chemotherapy selectively in your patient population. Do you think that either local control or survival would have been improved with a more consistent use of postsurgical chemotherapy?

And then finally, do you have any data on the relationship of these patients to their pretreatment T stage?

Thank you.

Rodrigo O. Perez, M.D. (São Paulo, Brazil): Dr. Beart, thank you for those kind words and for those excellent questions. I will try to address each one of them.

The first one, our 5-year local recurrence rate was about 14%. It is true that local recurrences did not significantly correlate with the presence of lymph node metastases in our series. Actually, the only risk factor for local recurrence in our study was the presence of perineural invasion, which was quite surprising. What we think is that this is an effect of radical surgery. Removing lymph nodes by total mesorectal excision leads to some lymph node positivity. However, excision of such lymph nodes probably prevents local recurrences in a subset of these patients, and this is why we believe that lymph node metastasis was not correlated with local recurrence after radical surgery. Now, our main concern was that if we had left those positive lymph nodes behind, a subset of these patients would probably develop local recurrences, and in this setting, the presence of lymph node metastasis would possibly become a significant prognostic factor and a significant predictor for local recurrence.

The second question, which is very interesting, regards the interval period between chemoradiation therapy and surgery. We were very much concerned if delayed surgery did have any impact on survival. Actually, we did present a paper at the SSO annual meeting this year, also in Washington, which looked into that. We found that the patients that had delayed surgery, for whatever reason, between chemoradiation therapy and surgery, final survival rates, either overall or disease-free survival, were similar, and this delayed surgery was not harming them.

The third question is about the management of local recurrences. I can say that three out of eight patients in this series with local recurrences were salvaged. Of these three, all were after anterior resections and two of them were endoluminal recurrences and only one was with an extra-rectal recurrence.

About chemotherapy, I do agree with you that we did selectively use chemotherapy in these patients, as it is currently recommended that patients with stage III disease, that is, with the presence of lymph node metastasis, require, or there are some data indicating that these patients benefit from chemotherapy, and this is our current recommendation. So patients with positive lymph nodes did get some adjuvant therapy as opposed to those with no lymph node metastasis who did not get any adjuvant therapy. I am not sure if giving all these patients chemotherapy would have helped any in terms of local recurrence rates, even though some benefit could be expected for systemic recurrences. Still, I am not sure there are enough data to support that giving all of these patients with ypT2N0 rectal cancer might be of any benefit. We might have to look for other risk factors, and probably some molecular markers might help us in that way.

Finally, to answer the question of pretreatment staging, I do agree with you, that downstaging might reflect tumor behavior in a way that patients that were T4s or T3 before chemoradiation therapy and became ypT2 may be better than the ones that were T2 and remained T2 after chemoradiation therapy. And it is not easy to accurately document that. Some colorectal surgeons still feel that they do better with the finger than with other radiological studies such as endorectal ultrasound for T staging. Still, we do think that the main question here, if we are going to consider local excision, is the lymph node status, and staging of lymph nodes either pre-chemoradiation or post-chemoradiation is quite difficult. In our study, we did not have the data on endorectal ultrasound of all patients. We did have the data on CT scans as pretreatment staging, and I can say that did not correlate with the presence of lymph node metastasis or with survival. However, we should look into that more carefully prospectively.

Thank you once again.

Alessandro Fichera, M.D. (Chicago, IL): I enjoyed your presentation, as I often do with work presented by your group. If I have understood your data correctly, the incidence of positive lymph nodes was lower if the patient had a longer interval between the treatment and the surgery, and this is a very interesting point. Julio Garcia-Aguilar is conducting a trial at UCSF and we have now started enrolling patients in the longer interval arm. Based on this information, these data, and these assumptions, I am not sure that your conclusion that if you do a local excision in these patients you would have had higher recurrence rates is valid. Indeed

we don't know what happens to these lymph nodes if you do wait longer or if you don't touch them by doing just a local excision. So it would be interesting to look at that, and hopefully Julio will help us find the answer, but I am afraid your conclusion may not be in the future completely on target.

I have truly enjoyed your presentation.

Dr. Perez: I do agree with you. We have tried to set up a trial to study that as well. We have an ongoing trial, which is open for accrual in Brazil, and is recruiting patients with distal rectal cancer undergoing neoadjuvant chemoradiation therapy. We are performing PET-CT in a sequential fashion. Patients undergo a baseline PET-CT before chemoradiation, a second PET-CT after 6 weeks and an additional PETCT after 12 weeks. I can say that we do have additional downstaging with waiting a little longer. However, I am not sure how long is enough. Probably, after some point we might not get any benefit from waiting anymore. In our series, the mean interval between chemoradiation therapy and surgery is a little over 10 weeks for the whole group. Maybe, we will get to 12 weeks, but I am not sure we are going to get much longer than that. But I do agree with you, there might be a bias after a retrospective analysis.