Nonoperative Management of Rectal Cancer With Complete Clinical Response After Neoadjuvant Therapy

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Introduction: Nonoperative management (NOM) of rectal cancer after a complete clinical response (cCR) to neoadjuvant therapy is controversial. In this article, we retrospectively reviewed the outcomes of patients managed with selective NOM after a cCR to neoadjuvant treatment and compared these with patients who underwent standard rectal resection with a pathological complete response (pCR).

Methods: Patients completing neoadjuvant chemoradiotherapy (CRT) for stage I to III rectal cancer between January 2006 and August 2010 were retrospectively reviewed. Median follow-up was calculated in months after completion of CRT.

Results: Thirty-two patients (median follow-up 28 months) were treated by NOM after a cCR. Among 265 treated by CRT and rectal resection, 57 patients (22%) had a pCR and formed the control group (median follow-up 43 months). Factors associated with selective use of NOM included lower pretreatment stage, older age, and distal tumor location ($P < 0.05$). In the NOM group, 6 recurred locally (median 11 months, range 7–14), 3 of whom also had concurrent distant recurrence. All 6 local failures were controlled by salvage rectal resection with no further local recurrence of disease (median follow-up 17 months). In the rectal resection/pCR group, there were no local failures. The 2-year distant disease-free survival (88% vs 98%, $P = 0.27$) and overall survival (96% vs 100%, $P = 0.56$) were similar for NOM and rectal resection/pCR groups.

Conclusions: Rectal resection was successfully avoided in 81% of patients selected for NOM. When combined with salvage surgery, NOM appears to achieve similar local and distant disease control compared with patients with a pCR treated by rectal resection. Longer follow-up and prospective trials are warranted to evaluate this promising treatment option.

Keywords: complete clinical response, neoadjuvant therapy, rectal cancer

(*Ann Surg* 2012;256: 965–972)

The standard management for the approximately 39,000 patients who develop rectal cancer annually in the United States consists of neoadjuvant chemoradiotherapy (CRT) followed by rectal resection with total mesorectal excision (TME) and adjuvant chemotherapy for stage II and III cancers, whereas patients with stage I disease are generally treated by surgery alone.[1] For those patients who receive neoadjuvant CRT, a significant proportion (15%–40%) will achieve a pathological complete response (pCR), in which pathologic examination of the surgical specimen reveals no viable tumor cells.[2–4] Patients who achieve a pCR have a favorable prognosis, with local recurrence (LR) rates close to zero and 5-year survival rates of greater than 95%.[5,6] This raises a question: In the absence of residual tumor, can patients be managed successfully without surgery so as to spare them the perioperative and long-term morbidity of rectal resection?[7,8]

Evidence that primary radiotherapy with or without chemotherapy can be curative in rectal cancer has been reported in a series that used primary radiotherapy for patients with severe medical comorbidities, with unresectable tumors, or who refused operation. Although the majority of rectal cancers recurred, the patients who presented with mobile tumors achieved a 10-year survival rate of 17%.[9] The same institution also showed that tumor regression after radiotherapy is time-dependent, with an increasing period of observation associated with a higher rate of complete clinical response (cCR).[10]

The first prospective "watch and wait" approach for nonoperative management (NOM) of rectal cancers with a cCR after neoadjuvant CRT was developed by Habr-Gama et al in São Paulo, Brazil. Patients are assessed for clinical response 8 to 10 weeks after completion of neoadjuvant CRT, and those with evidence of residual tumor are advised to have surgery. The remaining patients, those with a cCR, are monitored closely for an additional 10 months, and those who have a sustained cCR at 1 year after completion of neoadjuvant CRT are offered NOM. In their seminal manuscript, published in 2004, Habr-Gama et al[4] reported 5-year overall survival (OS) and disease-free survival (DFS) rates of 100% and 92% and LR rates of 3% among 71 NOM patients. The approach is now under investigation at multiple international sites; a recent article by Maas et al in Maastricht, The Netherlands, confirmed the efficacy of an observational approach that employed magnetic resonance imaging (MRI) and endoscopic examination for clinical response evaluation.[11]

Over the past 6 years, a small number of select rectal cancer patients have been treated by NOM at our institution after they were found to have a cCR after neoadjuvant CRT. The aim of this retrospective review was to report the oncologic outcomes of patients treated with NOM at our institution and compare them to patients who attained a pCR after neoadjuvant CRT and rectal resection.

METHODS

Rectal Cancer Patients

After approval from the institutional review board at Memorial Sloan-Kettering Cancer Center, data were extracted from prospective databases, interviews with surgical staff, and the electronic medical records of patients with rectal cancer treated at the institution from January 2006 to August 2010. Only patients with localized, biopsy-proven adenocarcinoma of the rectum who received long-course CRT over 5 to 6 weeks using external beam radiation plus 5-fluorouracil (5-FU) or capecitabine were considered for this review. Patients who presented with distant metastasis were excluded. The vast majority of patients were staged at presentation with endorectal ultrasonography and computed tomography (CT) of the chest, abdomen, and pelvis. Neoadjuvant CRT was given for locally advanced cancer, ultrasound-staged T3 or T4 (uT3/4) or ultrasound node-positive (uN1/2) tumors,

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Disclosure: The authors declare no conflicts of interest.

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ISSN: 0003-4932/12/25606-0965
DOI: 10.1097/SLA.0b013e3182759f1c

or for distally located uT2 tumors to improve the probability of a sphincter-sparing resection.

NOM Group

Patients who were managed nonoperatively after a cCR to neoadjuvant CRT were identified by surgeon recall by the 6 attendings on the colorectal surgery service. Patients were excluded if the pathologic diagnosis of rectal adenocarcinoma was unproven, if their primary tumor was treated before or after CRT by local excision, if they received neoadjuvant chemotherapy alone, or if they failed to achieve a cCR (eg, patients who had an incomplete clinical response but were treated nonoperatively because of severe cardiovascular, pulmonary, or neurologic disabilities or because of patient refusal of surgery).

Thirty-two patients were identified who were treated with NOM. Twenty (63%) received their neoadjuvant CRT at Memorial Sloan-Kettering Cancer Center. The median dose of radiotherapy administered was 5040 cGy (range 4500–5600 cGy). The timing and details of response assessment after CRT were not standardized in the NOM group. Patients were examined by their surgeon at 4 to 10 weeks after CRT. Response to treatment was gauged by a combination of digital examination, endoscopy, and selective biopsy of any residual mass or scar. MRI, CT, endorectal ultrasound, and carcinoembryonic antigen were obtained at the discretion of the treating physicians, but in this retrospective review, the results of imaging were not considered as criteria for cCR. In all 32 NOM cases, a cCR was documented by (1) no palpable tumor on digital rectal examination and (2) endoscopy showing no visible pathology other than a flat scar. Patients were counseled that NOM is not standard treatment and might compromise oncologic outcome. Patients then commenced close follow-up at the discretion of the treating physicians, which generally entailed physical examinations and flexible sigmoidoscopies every 3 months for the first year and every 4 to 6 months thereafter. Use of diagnostic imaging was not standardized, but included cross-sectional imaging every 6 months for the first 2 years for most patients. Neither endorectal ultrasound nor rectal MRI was used routinely.

pCR Group

For a comparative surgical group, we identified and reviewed patients who achieved a pCR after neoadjuvant CRT and rectal resection. A pCR was defined as no viable cancer cells identified by histologic examination of the rectal wall and rectal mesentery (ypT0N0).[12] Patients with a pCR are known to have a highly favorable prognosis and therefore set a high standard for oncologic outcomes.[2,13] Postoperative follow-up for the surgical patients was at the discretion of the treating physicians, but generally included digital and endoscopic examination of the rectum every 6 months and cross-sectional imaging every 6 to 12 months for the first 2 years.

Tumor Recurrence

Patients were censored for recurrence at the time of their last follow-up visit, which typically consisted of a history and physical examination, proctoscopy, and measurement of carcinoembryonic antigen levels. Recurrence was determined on the basis of the electronic medical records of all study patients, including surgeon and oncologist office notes, as well as endoscopy, radiology, operative and pathology reports. All patients found to have LR were evaluated by cross-sectional imaging to determine the presence or absence of concurrent distant recurrence (DR).

Statistical Analysis

The study endpoints included LR, DR, DFS, and OS. Time to recurrence was measured from the date of finishing neoadjuvant CRT to the time of first recurrence. DFS was defined as a patient free of disease at the time of last follow-up, and all patient deaths were counted as an event. Kaplan-Meier curves were utilized to estimate time-dependant rates of DR and LR. Survival distributions in the cohort were compared using the log-rank test, and illustrated with Kaplan-Meier curves. In addition, 2-year outcomes were reported in tabular format with the log-rank P value for the corresponding stratified survival distribution. Proportions of categorical variables were compared using the χ^2 test unless expected cell counts were less than 5, in which case the Fisher's exact test was used. Comparisons of mean values were calculated using the independent sample T test. Analyses were conducted using SAS version 9.1 (SAS Institute Inc, Cary, NC) and SPSS version 17.0 (SPSS, Chicago, IL).

RESULTS

The NOM group consisted of 32 patients with localized rectal cancer who achieved a cCR and were then managed nonoperatively by mutual decision between the patient and the treating physicians. Although in some instances strong patient resistance or refusal of surgery (N = 7), high medical comorbidity (N = 7), or concurrent resectable lung cancer (N = 1) influenced the decision to omit surgery, all NOM patients had a cCR and the majority of those who elected to pursue NOM, with the agreement of the treating physicians, were good candidates for surgical resection. For 30 patients, the decision to pursue NOM was made at 4 to 14 weeks after completion of CRT (median 6 weeks). For 1 patient, the decision was made when the patient presented for a second opinion regarding surgical management at 17 weeks. Another patient was found to have a cCR at 6 weeks, but the final decision for NOM was deferred until 25 weeks, when the patient had completed treatment for concurrent lung cancer. Adjuvant chemotherapy was given to 17 patients (53%), 15 patients received FOLFOX, 1 CAPOX, and 1 5-FU and leucovorin. Median follow-up for the NOM group was 28 months (range 9–70 months)

For the comparative pCR group, the surgical pathology reports of 265 patients treated by neoadjuvant CRT, followed by rectal resection according to the principles of TME, were reviewed, resulting in 57 (22%) pCR patients. The median time to surgery after CRT for these 57 pCR patients was 6.9 weeks (range 5–17 weeks). Because of variable intervals of post-CRT assessment and inconsistent documentation of post-CRT physical examination and endoscopic findings, it was not possible to retrospectively determine the number of pCR patients who met criteria for cCR on preoperative assessment. Adjuvant chemotherapy was given to 50 patients (88%) in the pCR group. The median follow-up for the pCR patients was 42 months (range 1–70 months).

To better understand the spectrum of patients treated nonoperatively, we compared the clinical characteristics of the NOM and pCR groups (Table 1). Patients in the NOM group were significantly older ($P = 0.009$) and presented with tumors that were of lower clinical stage ($P = 0.011$) located closer to the anal verge ($P = 0.02$). Although more NOM patients had significant medical comorbidities than pCR patients, this did not reach statistical significance (47% vs 28%, $P = 0.07$).

Tumor Recurrence and Surgical Salvage

Of the group treated with NOM, 6 patients developed LR at a median time of 11 months (range 7–14 months, Table 2). Three of these patients also developed DR: 1 developed synchronous lung metastases at 11 months, another developed metachronous lung and liver metastases at 22 months, and 1 developed lung metastases at 28 months. The 26 NOM patients with sustained local control have also remained free of distant disease. All 6 local failures were controlled by salvage rectal resection and TME, with no further LR of disease at a median follow-up of 17 months. Three patients had low anterior

resection (LAR) and 3 had abdominoperineal resection (APR) for salvage; 5 out of 6 salvage operations achieved an R0 resection. Currently the 3 patients who recurred locally only are free of disease. Among the 3 patients who recurred locally and distantly, 2 are alive with disease and 1 patient died of distant disease. In the pCR group, there were no LRs but 3 patients developed distant metastases (all lung) at a median time of 25 months (range 19–32). One patient had resection of the lung metastases and currently has no evidence of disease, whereas the other 2 patients died of their disease.

TABLE 1. Clinical Characteristics of Patients in NOM Group Compared With pCR Group

	NOM Group	pCR Group	*P*
Patient (n)	32	57	
Age (median in years)	70	60	0.009*
Sex			
Male	18 (56%)	27 (47%)	0.42†
Female	14 (44%)	30 (53%)	
Cigarette smoking			
No	25 (78%)	47 (82%)	0.88†
Former	4 (13%)	6 (11%)	
Yes	3 (9%)	4 (7%)	
Cardiovascular disease			
Yes	7 (22%)	9 (16%)	0.47†
No	25 (78%)	48 (84%)	
Respiratory disease			
Yes	5 (16%)	3 (5%)	0.10†
No	27 (84%)	54 (95%)	
Diabetes mellitus			
Yes	5 (16%)	5 (8%)	0.33†
No	27 (84%)	52 (92%)	
Any pretreatment morbidity			
Yes	15 (47%)	16 (28%)	0.07†
No	17 (53%)	41 (72%)	
Distance from the anal verge (range), cm	6 (0.5–12)	7 (2–12)	0.02*
rT stage			
3	22 (69%)	39 (78%)	0.34†
2	10 (31%)	11 (22%)	
rN stage			
Positive	18 (56%)	31 (61%)	0.67†
Negative	14 (44%)	20 (39%)	
Overall pretreatment stage			
III	18 (50%)	31 (61%)	0.011†
II	6 (25%)	18 (35%)	
I	8 (25%)	2 (4%)	

*Difference in the mean, independent sample *t* test.
†χ^2 test.

Patient Outcomes

When we compare the NOM group with the pCR group, there is a higher rate of LR in the NOM group (2-year actuarial rate of LR: 21% vs 0%, $P = 0.001$, Table 3, Figure 1). However, the 2-year rates of DR (8% vs 2%, $P = 0.30$), DFS (88% vs 98%, $P = 0.27$), and OS (97% vs 100%, $P = 0.56$) are similar and favorable in both groups.

DISCUSSION

Our adoption of the selective use of NOM has evolved from our long institutional experience with neoadjuvant CRT for locally advanced rectal cancer.[14–16] In addition, the pursuit of this approach has been inspired by the pioneering work of Habr-Gama et al,[4] who have demonstrated the safety of deferring surgery for patients who achieve a cCR.[17] In this retrospective series, each decision to omit surgery in patients with a cCR was reached jointly after a lengthy discussion about risks and benefits. NOM was presented as a departure from standard management, and was not done under the direction of a standardized policy. In some cases, the decision was influenced by the patient's advanced age, severe medical comorbidity, or strong resistance to surgery of the patient. However, in about half of the patients, the primary motivation was simply to avoid the long-term morbidity of a rectal resection and to attempt an alternative treatment strategy that appeared to offer a similar chance for cure. Our experience confirms that in well-selected patients, the Habr-Gama's "watch and wait" strategy is readily accepted by patients and appears to have good intermediate-term results.

One of the major concerns about NOM for rectal cancer is the inherent difficulty of assessing the degree of tumor regression after CRT. It is well known that pCR will occur in 15% to 40% of patients with rectal cancer treated with neoadjuvant CRT, but published data and expert opinion, including reports from our institution, are mixed as to whether cCR can accurately predict pCR.[3,18] In our NOM patients, cCR was determined almost entirely by digital rectal examination and endoscopic visualization. After a median of 28 months of follow-up, only 6 of 32 patients developed LR. Our data therefore support the idea that direct examination of the primary tumor may be sufficient to determine a cCR. Conversely, high-resolution imaging to evaluate the primary tumor and regional lymph nodes (LN) may not

TABLE 3. Two Year Outcomes Comparing Patients Treated With NOM and Those With a Rectal Resection (RR) and pCR

Factor	NOM	RR/pCR	*P*
LR	21%	0	<0.001
DR	8%	2%	0.30
DFS	88%	98%	0.27
OS	96%	100%	0.56

TABLE 2. NOM Patients Who Developed LR

Pretreatment Clinical Stage		Recurrent Disease			Surgical Stage			
T	N	Time to	Type of	Surgery	ypT	ypN	Margin	Survival Status
2	0	11 m	Mucosal	APR	3	0	R0	AWD
3	0	12 m	Mucosal	APR	3	1	R0	AWD
3	1	13 m	Mucosal	LAR	2	0	R0	NED
2	X	10 m	Mucosal	LAR	3	0	R0	NED
2	1	7 m	Mucosal	TAE then APR	3	2	R1	DOD
3	2	14 m	Nodal	LAR	0	1	R0	NED

AWD indicates alive with disease; DOD, dead of disease; NED, no evidence of disease.

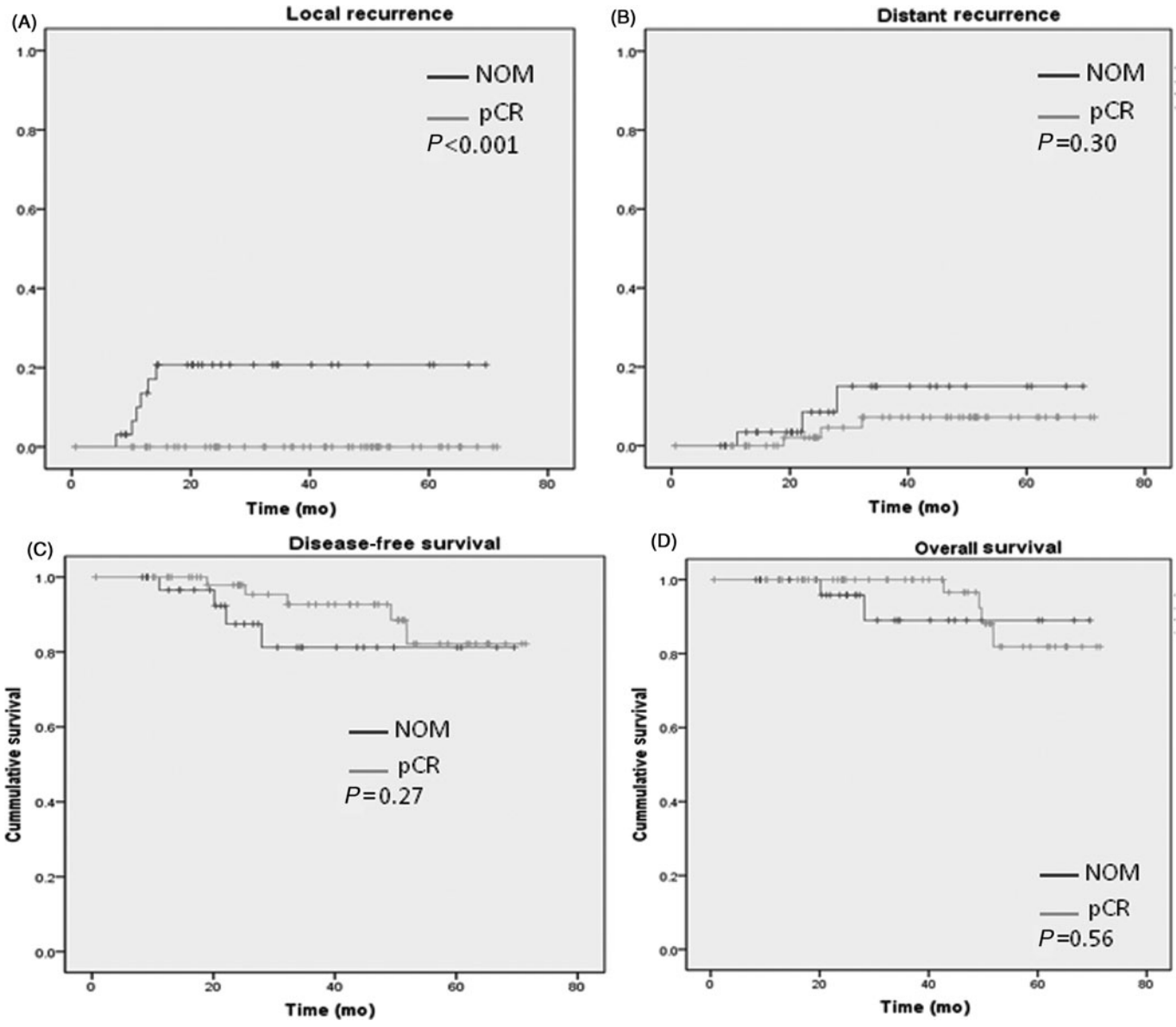

FIGURE 1. Kaplan-Meier curves comparing outcomes of NOM versus rectal resection/pCR. A, LR. B, DR. C, DFS. D, OS.

be essential for patient selection, because effective CRT that destroys the primary tumor might also destroy all regional disease.

Our experience suggests that the critical factors for case selection are (1) to adopt highly stringent criteria for cCR based on digital examination and endoscopic visualization and (2) to defer final assessment of the favorably responding tumors for as long as 10 to 12 weeks after CRT so that tumors destined for pCR have sufficient time to involute to a bland, flat scar. During this critical assessment period, we often use a 2-stage strategy for response assessment. The patient is first seen at 6 to 7 weeks. Patients who have achieved a convincing cCR may begin posttreatment monitoring or proceed with adjuvant chemotherapy; in addition, patients with suboptimal responses that will never qualify for NOM may proceed with surgery. Patients with major tumor responses that fall slightly short of criteria for cCR are asked to return for a second response assessment at 10 to 12 weeks. Thus, tumors that retain small areas of induration, nodularity, or ulceration on the first assessment are given more time to evolve. Only when the tumor site regresses to nothing more than a pale, flat scar with or without telangiectasias should the tumor be labeled as a cCR.[11,17,19] We believe a 2-stage (or multistage) response assessment strategy is efficient and allows the "test of time" to work in favor of patients who achieve major tumor regression, while not burdening average-to-poor responders with long waiting periods. In our experience, surface biopsies of the scar are rarely helpful and in some cases can be misleading. Of note, these principles of close monitoring of tumor regression by direct examination without routine use of biopsy are currently used in the management of anal cancer.[20]

Building on Habr-Gama's pioneering work, 2 series of patients treated nonoperatively after CRT have recently been published. Maas et al[2] from Maastricht reported 21 patients with a median follow-up of 25 months who were screened carefully by high-resolution MRI before and after CRT. Patients suspected to have regional LN

metastases were excluded. Oncologic results for these highly selected patients have been outstanding, with only one LR and no DRs.[11] Dalton et al[9] from Exeter reported 6 patients who were selected by clinical examination and MRI; no tumor recurrences have been detected after median follow-up of 28 months. These exceptionally good results are the first published data to provide evidence that imaging may improve patient selection for NOM.[19]

Once patients with cCR are selected, the second critical aspect of NOM is close monitoring for local tumor recurrence. Our data show that isolated LR is the most common type of relapse, and suggest the critical time frame is the first 14 months after CRT. Examinations with both clinical and endoscopic evaluation of the rectum during this period are mandatory. This time period also appeared to be the critical time for recurrence in the Habr-Gama series. They reported that 23 (82%) out of the 28 patients who recurred after initial cCR at 8 weeks post-CRT did so within the first year. The late recurrences occurred at 18, 43, 56, 64, and 79 months, all of which were endoluminal. The one recurrence in the Maastricht series was endoluminal and occurred 22 months posttreatment. On the basis of these data, the yield of frequent imaging during follow-up to supplement direct examination appears to be low. Because of fibrosis associated with radiotherapy treatment, cross-sectional imaging can be unreliable in detecting residual or recurrent local disease.[21,22] However, the recent use of high-quality diffusion-weighted MRI, such as that used in the Maastricht study, has shown promise in identifying cCR, and may also be useful in detecting recurrent pelvic disease.[23]

Of the 6 patients who recurred locally in our series, 5 recurred endoluminally. The one patient who recurred with nodal disease in the pelvis had extensive nodal disease on presentation both with endorectal ultrasonography and CT of the pelvis. The patient's primary tumor disappeared after CRT, and the patient refused surgery. This single case suggests that extensive nodal disease may be a contraindication to NOM. All 6 of the local failures were amenable to salvage surgery, with an R0 resection in 5. Three patients needed an APR and 3 patients were salvaged with an LAR. The one patient who had an R1 APR developed rapid regrowth of the rectal tumor at 7 months, insisted on local excision as the first salvage procedure, continued to refuse APR for several more months despite continued local tumor growth, and ultimately died from metastatic disease 12 months after salvage APR.

Of note, we have seen no LRs after salvage by radical surgery (median follow-up 17 months). On the contrary, DR developed in 3 of the 6 patients. Our experience thus far strongly supports the benefit of salvage surgery and the need for careful monitoring of the rectum.

The results from this study are constrained by all the inherent flaws and biases of a retrospective study. The selection criteria for NOM were not standardized, there is variable use of adjuvant chemotherapy, the comparative groups were imbalanced in location and stage of disease, and there may have been recall bias in identifying patients. Nevertheless, we believe our outcome data for NOM are encouraging and justify prospective evaluation in larger studies.

The ideal trial design to assess the efficacy and safety of NOM would be a randomized clinical trial comparing this approach with the standard approach of neoadjuvant CRT followed by rectal resection according to the principles of TME. However, accrual to such a trial would likely be difficult, as many patients would resist random assignment to radical surgery when presented with the alternative option of NOM. High-quality phase II trials are, however, highly feasible given the enthusiasm most patients express for NOM. It is relevant to note that the "watch-and-wait" approach after CRT became the standard of care for squamous cell carcinoma of the anal canal, without being subjected to a randomized trial.[24]

CONCLUSIONS

The selective use of NOM for patients with rectal cancer who achieve a cCR after neoadjuvant CRT appears to achieve similar oncologic outcomes to patients who are found to have a pCR after neoadjuvant CRT and rectal resection, while conferring the advantage of avoiding the morbidity of a rectal resection. Further prospective studies are needed to evaluate this promising treatment option.

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DISCUSSANTS

R. D. Madoff (Minneapolis, MN):

In the past 20 years, consensus on how to approach rectal cancer has gelled. This consensus was driven largely by improved imaging, particularly ultrasonography and MRI, which really allow us to know exactly what kind of tumor we are dealing with before we begin treatment. We now very clearly understand the importance of surgical technique for optimizing results, and, with the improved imaging, we are seeing a great increase in the number of patients who receive neoadjuvant chemoradiation before they are treated. Unfortunately, patients who undergo radical surgery with radiation suffer a significant amount of morbidity, and, very frequently, poor functional results, what we now call "low anterior resection syndrome."

Fifteen percent to 20% of patients who receive chemoradiation enjoy a complete response. What do we do about these patients? The tradition has always been to resect the site of the primary tumor, and, in fact, there is often enough microscopic evidence of residual disease to justify this approach.

About 20 years ago, Professor Habr-Gama came up with the idea that radical resection was perhaps too much surgery to offer to patients with no cancer left, and she began her "wait and see" approach. Suddenly, surgeons in this field, who are very mindful of the Nigro approach to anal cancer, and who eliminated the need for surgery in patients with a complete response, began to wonder if a similar approach might indeed apply to rectal cancer. Should we just radiate, give chemotherapy, and observe, rather than operate on complete responders? The data presented today largely confirm what we know from Professor Habr-Gama, but raise a number of questions.

First, clinically complete response was defined by physical examination and endoscopy. Imaging, particularly the advanced imaging, was at the discretion of the surgeon. What was the policy with respect to suspicious nodes seen on MRI, CT, or ultrasonography? What happens to patients who have persisting nodes after they receive this treatment? You do not routinely perform advanced imaging. Are they still eligible for operation?

Second, you reported 6 cases of LR, 5 of whom were able to have an R0 resection. If you think about the parallel experience of local excision for rectal cancer, the salvage rate after failed local therapy is low, 50% for most surgeons. So, what is different in this situation, and what is the risk of losing in the salvage concept?

Third, looking toward the future, how should these patients be followed, as there has not been a clear protocol for imaging posttreatment? Should these patients have MRI, diffusion-weighted MRI, or PET (positron emission tomography) CT?

Finally, 25% of the patients who were treated nonoperatively had stage I disease. Are we going about the treatment of rectal cancer entirely backwards? Should we be irradiating more favorable lesions upfront and saving surgery only for those who fail to respond?

Response from P. Paty:

Let me recap your 4 questions.

First, you asked about the importance of nodal disease on imaging, both at the time of presentation and the time of assessment of complete clinical response.

I do not think we can answer that question from our retrospective data. This would require a prospective trial because we do not have any information about the patients who were considered for NOM but rejected on the basis of persistent nodal disease or other findings that the surgeon felt uncomfortable with.

However, I can say that half of the patients in the NOM group were staged as node-positive on presentation, and I think the rationale that Dr Habr-Gama and others have used, as goes the primary tumor, so goes the nodal disease. In patients who do not have extremely bulky nodal disease or extensive nodal disease, the expectation is that the bulkiest tumor in the rectal wall will be the defining factor in terms of how the nodal disease will respond, but I cannot truly answer your question because we do not have the entire denominator or sufficient number of cases.

Your second question was about the LRs; what is the efficacy of surgical salvage? I think there are 2 points that need to be made. First, nearly all of the recurrences occur in the rectal wall. They are detectable on physical examination, and they are generally resectable.

What is different with transanal excision is that you are mainly concerned about residual or recurrent nodal disease, which is more difficult to detect than disease recurrence in the rectal wall. So, although we do not have enough cases or enough long-term follow-up to be sure, my suspicion is that surgical salvage of LR in the nonoperative setting will be more effective than following transanal excision, where occult nodal disease is very hard to monitor. I would also say that even in our small experience of 6 LRs, in the patients who recur, tumors tend to be aggressive. Among 6 local failures, 3 developed distant disease within months of local failure. So, I think that some of the tumors that recur locally may have aggressive biology. Despite a high rate of R0 surgical salvage, LR is likely to be a negative prognostic factor for long-term survival, but I would argue that the patients who developed distant metastases were probably at high risk even if they had been operated on upfront.

It is a complicated question, but I believe close monitoring and aggressive surgical salvage is critical if you plan to practice NOM.

You mentioned follow-up testing; what is required in the surveillance period after you have committed to NOM? The one thing we do know is the critical importance of examining patients frequently in the first 18 months after radiation. That is the high-risk period. If residual viable cancer exists in the rectal wall, it is likely to regrow within 18 months.

In my experience, examination exceeds imaging in sensitivity by an order of magnitude. On examination, you can monitor the scar. You can take photos of it. You can see subtle changes if you are diligent in your record-keeping and follow-up. However, as far as what imaging is needed or how often, I do not think we know what is optimal. In our practice, we imaged patients mainly for monitoring of DR, and we were monitoring at 6-month intervals.

Your last question was whether stage I rectal cancer patients are appropriate for this type of management? It is a good question that will only be answered over time as more experience accumulates. One interesting aspect about this data is that if we adopt NOM more broadly, the patients who are most likely to be cured are the ones with early cancers. So, we may be irradiating the advanced cancers to make them more resectable and irradiating the earlier cancers to avoid operation. If we embrace this paradigm fully, it will change how we manage the entire spectrum of rectal cancer patients.

DISCUSSANTS

J. Daly (Philadelphia, PA):

Can you tell us anything about the tumor characteristics of the patients who were managed nonoperatively, other than stage histologic characteristics, for example? In those patients who are managed

nonoperatively, in which you thought you achieved a complete clinical response, were there any fine needle aspirations or biopsies; was anything at all done to verify that this response produced some pathologic correlate clinically?

Third, your median follow-up is relatively short at 17 months to 26 months. Clearly, a longer follow-up would be beneficial. Some of these patients may recur beyond the standard 18 months that you just described after radiation and chemotherapy. Can you tell us anything as to what has happened with these groups of patients?

My last question refers also to disease-free interval. Could you clarify the median follow-up for these patients, because one would assume there still will be disease recurrence over time? Can you estimate what that may be, from other studies that you have conducted retrospectively at Sloan-Kettering?

Response from P. Paty:

The first question was the characteristics of the tumors that are treated. We reviewed all the charts and looked at as many data points as possible. The most significant finding was that patients who achieved a complete clinical response and were managed nonoperatively tended to have smaller tumors that were located low in the rectum.

These are not big, circumferential, obstructing tumors. They tend not to have advanced nodal disease. They tend to be cancers that are lower in the rectum, where we're more concerned about low reconstructions or permanent stomas. These characteristics were statistically significant when compared with the pathological CR group. Also, in our series, the nonoperative patients were somewhat more likely to have medical comorbidities that made us worry about the risks of operation.

That is about the best I can tell you from the data. What are not represented in this series are the large, high-risk, high-grade infiltrative tumors. Tumors that grow largely submucosally, as high-grade tumors often do, are poor candidates for this, because you don't have much to look at or measure to assess response to chemoradiation. So, these should generally be tumors that can be seen endoluminally and monitored.

In our series, the use of biopsies to assess response to radiation was completely nonstandardized. My experience is that biopsies can be misleading. You can biopsy microscopic disease that's going to regress, or you can certainly miss viable disease that will survive. And there's other data from my colleague, Dr Julio Garcia-Aguilar, in his prospective studies, showing that surface biopsies are likely to be low yield. Most of the residual tumor after chemoradiation lies in the muscular wall or deeper.

So, if you are going to biopsy, you have to biopsy deep. So, the role of biopsy is not well defined. The most important thing is seeing the gross regression of the tumor.

Finally, about follow-up, you are absolutely right. I think longer-term follow-up is absolutely essential. Dr Habr-Gama has shown there are late failures locoregionally, but I don't think we know how high that number is. I'm encouraged by the Princess Margaret data, which has more than 20-year follow-up on some patients. They had 20-year survivors treated by radiation alone. So, I think many of the responses will be durable.

DISCUSSANTS

F. Michelassi (New York, NY):

The authors have tried to validate a nonsurgical approach to low rectal cancer patients who achieve complete clinical response after neoadjuvant therapy. We know that complete pathologic response occurs in 25% to 30% of cases. It would be great if we knew how to select these patients and avoid operating on them. We all have been in a difficult position of having to explain to a patient, after a surgical resection that may have condemned them to a permanent stoma and lifelong functional disturbances, that there was absolutely no cancer in the specimen because it had been completely eliminated by radiation therapy and chemotherapy preoperatively.

We are all worried about the presence of unrecognized nodal disease. Obviously, recurrent mucosal disease is easy to detect on physical and endoscopic examination, but nodal disease may be more difficult. Looking at your data, you showed that 3 of your recurrences involved nodal disease, 2 in association with mucosal disease, and 1 without mucosal disease. The possibility exists that recurrent, or persistent, nodal disease is present in the absence of mucosal disease. How do you suggest that we follow these patients?

Also, do you have any functional data and quality-of-life data comparing these patients with the ones who undergo resection? There are functional disturbances after radiation therapy to the perineum, and these patients may develop proctitis, among other things that may be obvious.

All in all, this is a very promising treatment scheme, especially for early low rectal tumors, as you said, and I like the idea of considering this a trial for possibly delayed surgery rather than no surgery. The moment that recurrent disease occurs, obviously, we go to surgery. It will be important to know what the salvage rate is.

Response from P. Paty:

Let me just briefly answer your question about residual nodal disease despite complete regression of the primary tumor. This is a potential problem, but one that probably does not occur often. In the published series that evaluate extent of disease found in the resected specimen after chemoradiation, one important thing to look at with respect to residual nodal disease is the time interval from the completion of radiation to resection. Was the time interval long enough, which in my mind is 10 to 12 weeks, to assure a maximal response to chemoradiation? Most centers have reported data on tumors resected at 6 to 7 weeks, when the responses are still in evolution.

So, I think some of the published data can be misleading. If you wait and allow the full benefit of the radiation to occur, the correlation of ypT0 status in the wall and eradication of nodal disease is very high. In a pooled series of 3000 patients (Lancet Oncology 2010; 11:835–844), the risk of viable nodal disease in the setting of a ypT0 response in the rectal wall was only 5%.

On the other hand, patients who present with bulky advanced nodal disease are probably not good candidates for NOM, even when the primary tumor disappears with chemoradiation. These patients are difficult to cure even with surgery and probably should not be enrolled in this type of protocol.

Finally, you asked about quality of life. That is an excellent point. The whole point of NOM is to retain rectal function and quality of life for patients. We are performing a detailed study of our patients, led by my colleague Dr Larissa Temple.

DISCUSSANTS

R. Fry (Philadelphia, PA)

Dr Eberlein mentioned yesterday that Dr Eugene Bricker was a moral authority at Barnes Hospital, and I vividly remember Dr Bricker rising at a conference to say, "I would never remove a patient's rectum for a cancer that I could not see." I suspect that he would still say that today.

I would like to ask you about the selection of the endpoint for a complete response. These tumors regress and die over a period of time, and we are looking at a spectrum of tumor involution. A photograph you showed of a residual cancer was taken 8 weeks after completion of radiation therapy, but it looked to me like it was partially

responding. You operated on that patient at 8 weeks, whereas some of the patients were observed as long as 12 weeks before surgery. How do you determine when to declare a patient a failure with only a partial response? When do you know that with some patients, a tumor still present at 8 weeks may be completely gone at 12 weeks? How do you determine when to declare a failure, or when there is a complete clinical response?

Response from P. Paty:

I agree with you. The time-to-response assessment is a critical point in managing patients. I have come to realize that response assessment is probably optimized by a 2-stage type of assessment. Typically, we see patients at 6 or 7 weeks. If patients are clearly having a suboptimal response and there is a large bulky tumor remaining, it's certainly appropriate to plan for surgery. That patient is not going to achieve a complete response.

On the other hand, people who have had major tumor regression may have a small residual tumor or some subtle ulceration or nodularity. These are patients who are responding well. They can be sent home and asked to come back in a month for reassessment.

So, I'm not sure one point in time fits all patients. I think it needs to be a flexible assessment over a period of time, giving the benefit of the doubt to patients who have had major tumor regression.

DISCUSSANTS

A. Habr-Gama (Sao Paulo, Brazil):

Nowadays, we are more in favor of not operating immediately and our criteria for calling complete clinical response is almost the same as yours. Whenever we have some doubt, we always obtain a pelvic MRI. Or, more recently, when we are in doubt about a complete clinical response, we always perform a PET CT, because, in our experience, selection of these patients is very specialized.

If we delay operating, even when we see recurrence, we are not harming the patients. The majority of them do not need an operation, and I am very glad to see another paper last month in which you achieved the same survival result. Particularly regarding distal metastases, it is a very important criticism that when we leave a potential tumor, we may increase the rate of systemic metastases, but you achieved very good results, similar to what we and others have achieved.

Response from P. Paty:

Thank you for your comments.

DISCUSSANTS

E. Sigurdson (Philadelphia, PA):

In Warren Enker's paper, from your own institution, he presented data on patients who underwent local excision and then had pathological factors that put them at high risk for recurrence, but refused surgery. In that group, 50% were alive at 5 years and LRs were very high. Do you think that this is a different population? Or have our drugs improved, or how have things changed since Warren Enker presented his series some years ago?

Response from P. Paty:

The critical aspect for organ preservation in patients who are radiated is the response to radiation. The critical factor in local excision is the risk for spread into the mesentery. These are two different approaches in distinct patient populations.

It is obviously important in the radiated patients to select those patients for whom cancer has been sterilized from the primary tumor. And we don't know the risk factors to predict complete sterilization other than assessment of clinical response. We only had 6 local failures. But it's going to be tough to improve on clinical assessment, because, other than size and bulk of disease, I don't think we have anything that predicts very well how the tumor will respond to chemoradiation. You have to simply watch and follow.