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Nonoperative management after neoadjuvant therapy for rectal cancer: A single institution experience over 5 years

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A B S T R A C T

Background: Nonoperative or "watch and wait" strategies have emerged as a potential option for patients with rectal cancer that obtain a complete clinic response (cCR) after neoadjuvant therapy. We sought to evaluate our patients that experienced a cCR and their outcomes after non-operative management.

Methods: We performed a retrospective review of patients at our center with rectal cancer from 2012 to 2016. We then identified patients that had a documented "complete clinical response" of their tumors after different neoadjuvant treatments and underwent non-operative management. Patients were followed on a surveillance schedule that included physical exam, endoscopy and imaging.

Results: A total of 29 patients elected to undergo nonoperative management with a mean patient age of 67 years old. All patients were treated with neoadjuvant long course chemoradiotherapy. Seven patients were treated with initial induction chemotherapy followed by chemoradiation and 11 received consolidation chemotherapy. During a median follow-up of 27.6 months, there were 6 (21%) recurrences (1 = local, 1 = local and distant, 4 distant). Of the 6 total recurrences, 5 patients were candidates for salvage surgical resection.

Conclusion: Neoadjuvant treatment strategies may facilitate durable rates of cCR. Continued responses after these treatments could possibly enable more patients to undergo nonoperative management. We believe nonoperative management can be offered to patients seeking rectal preservation, but more research is required to select the appropriate patients. For those patients experiencing recurrence, the majority of patients can be salvaged surgically.

1. Introduction

Approximately 39,910 patients in the United States are expected to be diagnosed with rectal adenocarcinoma in 2017 [1]. A multimodal approach, to include varying combinations of surgery, chemotherapy and radiation is critical for achieving successful oncologic outcomes. Radical resection using the well-established technique of total mesorectal excision (TME) is the standard in treatment of these cancers [2]. Although surgical resection is the established standard of care in early rectal cancer and following chemoradiotherapy (CRT) in advanced disease, it is not without potential complications. Increased morbidity and mortality can occur as a result of an anastomotic leak which has a reported incidence between 1 and 13.68%. Other quality of life issues such as urinary/sexual dysfunction, incontinence, and low anterior resection syndrome are also well known risks of surgery [3,4].

More recently, there has been an increased interest in avoiding surgery in patients who have no evidence of disease after receiving chemotherapy and/or radiation. This phenomenon is commonly referred to as a complete clinical response (cCR) to neoadjuvant therapy. Avoiding surgery in patients with a cCR has several benefits but it does come with some degree of risk of local and/or distant recurrence in addition to the need for more frequent surveillance. Of course, the ability to avoid a major surgery allowing for rectal preservation is a significant advantage of this approach. The patients that do experience a local recurrence are frequently salvageable. Habr-Gama et al. first reported on the nonoperative management (NOM) of low rectal cancer after neoadjuvant chemoradiotherapy (CRT) and the concept of cCR. Of the 265 patients, 71 (26.8%) demonstrated a cCR after CRT for at least one year. At a median follow up of 57 months only two patients in the non-operative group experienced a local recurrence but were successfully salvaged with transanal excision or brachytherapy. There were no differences in systemic recurrences (3 in each group). Five-year overall and disease-free survival rates were 88% and 83%, respectively in resection group and 100% and 92% in non-operative group [5]. Other studies have since corroborated these findings with similar outcomes suggesting that carefully selected patients may be treated non-operatively [6–12]. However, there is limited prospective data with long-term follow-up of these patients which is highly relevant in the curative intent setting. The resulting uncertainty has prevented firm inclusion of non-operative management in treatment guidelines to date. There are

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also no reported means to accurately predict which patients will have a durable cCR.

Here we present our institutional experience with this evolving treatment paradigm. Non-operative management was discussed with every patient at their initial visit. In those that had a cCR, a well detailed informed discussion was had, and patients were then offered NOM as a treatment option.

2. Methods

This study was reviewed and approved by the Institutional Review Board at our institution. We performed a retrospective review from a prospectively collected database, of patients with rectal cancer at our institution from 2012 to 2016 who were managed with NOM after a cCR. To assess the response to neoadjuvant therapy, we used the previously described criteria for the diagnosis of cCR by Habr-Gama et al. which include: absence of ulceration, stricture, mass, or mucosal irregularity at clinical/endoscopic assessment, presence of mucosal whitening and telangiectasia. In addition to clinical assessment, radiographic imaging with computed tomography (CT), magnetic resonance imaging (MRI) or endorectal ultrasound (ERUS) was utilized for surveillance of locoregional and distant disease. We reported results of follow-up of these patients every 3–4 months for the first 2 years with physical exam, carcinoembryonic antigen (CEA), repeat lower endoscopy, and CT of the chest/abdomen/pelvis every 6 months. After 2 years, these patients were followed every 4–6 months. We included all patients that had a cCR during that time period that underwent NOM. Patient characteristics were reported using the mean, median, and standard deviation for continuous variables; and using frequencies and relative frequencies for categorical variables. Local recurrence and distant metastasis were confirmed pathologically. Time to recurrence (local, distant, or any) was summarized using standard Kaplan-Meier methods. All analyses were completed in SAS v9.4 (Cary, NC) at a significance level of 0.05.

3. Results

3.1. Patient characteristics

Twenty-nine patients diagnosed with rectal adenocarcinoma from 2012 to 2016 experienced a cCR after neoadjuvant therapy and were managed with a NOM approach. The average age was 67 years old with an equal distribution of male and female. Median follow-up for all patients were 27.6 months from time of diagnosis. Clinical and demographic characteristics were similar amongst all patients and are listed in Table 1. Eighty-eight percent of the cohort had low primary tumors (< 7 cm from anal verge) and 83% had at least a clinically staged T3 tumor determined by either MRI or rectal ERUS. Fifty-two percent of patients had clinically suspicious nodes on pre-therapy staging studies.

3.2. Treatment and recurrences

Twenty-two patients underwent initial neoadjuvant therapy using CRT with either Capecitabine or 5-Fluoruracil (5 FU) infusion and 11 of those patients received consolidation chemotherapy regimens after CRT was completed. In contrast, 7 patients received induction chemotherapy with FOLFOX followed by CRT. Two distant recurrences to the lung occurred at 8 months and 31 months in patients that were staged as T3N1 and T2N0, respectively. The former patient with distant disease to the lung was able to be successfully treated surgically and is still free of disease while the latter was not a surgical candidate. There was one distant recurrence to the liver in a patient initially staged as T3N0, 9 months after CRT alone. He underwent chemotherapy with FOLFOX/Bevacizumab prior to a successful liver resection and remains disease free. A distant isolated recurrence to an aortocaval node is currently being treated with SBRT (stereotactic body radiation therapy) 3 years after his diagnosis that was initially staged clinically as T3N2. Due to bulky adenopathy at the initial presentation, he underwent neoadjuvant FOLFOX followed by CRT. After experiencing his recurrence, he underwent additional chemotherapy to demonstrate stability of the aortocaval disease before SBRT.

Table 1
Patient demographics and tumor information.

		Overall
Overall	N	29 (100%)
Age at Diagnosis	Mean/Std/N	67.4/14.3/29
	Median/Min/Max	69.8/41.3/92.3
Gender	Male	13 (44.8%)
	Female	16 (55.2%)
Coronary Artery Disease	Yes	7 (24.1%)
Hypertension	Yes	15 (51.7%)
Diabetes	Yes	6 (20.7%)
Body Mass Index (BMI)	Mean/Std/N	28.3/4.8/29
	Median/Min/Max	27.2/19.0/38.2
Baseline CEA	Mean/Std/N	2.2/1.5/26
	Median/Min/Max	1.7/0.5/5.1
Pathology	Well	5 (17.2%)
	Moderate	21 (72.4%)
	Poorly	2 (6.9%)
	Unknown	1 (3.4%)
Location in rectum from anal verge	Lower < 7 cm	23 (79.3%)
	Middle 7–11 cm	5 (17.2%)
	Upper 12–15 cm	1 (3.4%)
T Stage	T2	5 (17.2%)
	T3	24 (82.8%)
N Stage	N0	14 (48.3%)
	N1,2+	13 (44.8%)
	Unknown	2 (6.9%)
Chemotherapy (induction and consolidation)	None	11 (37.9%)
	Induction	7 (24.1%)
	Consolidation	11 (37.9%)

Concurrent local recurrence and distant liver metastasis occurred in one patient at 13 months who was initially staged clinically as a T3N1. He received CRT followed by consolidation chemotherapy with CAPOX prior to detection of a synchronous recurrence. This individual was then able to be salvaged with a synchronous R0 liver resection and abdominoperineal resection (APR) followed by 5 FU and Bevacizumab and remains free of disease. Final pathology returned as ypT3N0M1a.

One isolated local recurrence occurred in a clinically staged T2N0 patient that underwent CRT 2.5 years after his diagnosis on surveillance endoscopy. Staging workup for the local recurrence did not demonstrate any metastatic disease and he is currently being scheduled for salvage low anterior resection (LAR).

Of the 6 total patients that had either a local, local/distant, or distal alone recurrence of disease after neoadjuvant therapy, 4 were able to be surgically salvaged. There was one death in the cohort that was attributed to causes unrelated to rectal cancer. No clinically significant differences were seen between the local, distant, or synchronous recurrence in relation to patient characteristics, tumor stage, different treatments regimens, pathology, etc (Tables 1 and 2). The recurrence-free survival curves for local, distal and any recurrences are illustrated in Fig. 1a–c. The median follow-up was 27.6 months (range: 5.5–64.5 months) and the median recurrence times were not reached. The 1-year local, distant, and any recurrence rates were 0.95 (95% CI: 0.72, 0.99), 0.89 (95% CI: 0.69, 0.96), and 0.89 (95% CI: 0.69, 0.96), respectively. The 3-year local, distant, and any recurrence rates were 0.87 (95% CI: 0.54, 0.97), 0.76 (95% CI: 0.49, 0.90), and 0.68 (95% CI: 0.40, 0.85), respectively (Table 3).

Table 2
Patient staging and treatment Outcomes.

Patient	Sex	Age	Location of tumor	TNM staging	Pre-therapy CT staging results	CRT (50Gy)	Chemo? Consolidation or induction	Local Recurrence	Distant Recurrence after cCR	Alive	Alive with disease	Treatment of recurrence
1	Male	78	Low	cT3N0	no mets	CRT with Capecitabine	no	none	none	yes		
2	Female	78	Low	cT3N1	no mets	CRT with Capecitabine	no	none	none	yes		
3	Female	51	High	cT3N1	no mets	CRT with 5 FU	Consolidation chemo with FOLFIRI (4 cycles)	none	none	yes		
4	Female	88	Low	cT3N1	no mets	CRT with 5 FU	Consolidation chemo with 5 FU, Leucovorin (8 cycles)	none	none	yes		
5	Male	79	Low	cT3N1	no mets	CRT with Capecitabine	Consolidation chemo with FOLFOX (8 cycles)	none	Lung, 15 months	yes		Lung metastasectomy
6	Female	44	Low	cT2N0	no mets	CRT with 5 FU	Consolidation chemo with 5 FU, Leucovorin (8 cycles)	none	none	yes		
7	Female	78	Low	cT3N1	no mets	CRT with Capecitabine	Consolidation chemo with Capecitabine (6 cycles)	none	none	yes		
8	Female	89	Low	cT3N0	no mets	CRT with Capecitabine	no	none	none	yes		
9	Female	78	Middle	cT3N0	no mets	CRT with Capecitabine	Consolidation chemo with Capecitabine (6 cycles)	none	none	Yes		
10	Female	79	Low	cT3N1	no mets	CRT with Capecitabine	no	none	none	Yes		
11	Female	79	Low	cT2N0	no mets	CRT with Capecitabine	no	none	Lung, 7 months	yes	yes	Additional chemotherapy
12	Male	59	low	cT3N2	no mets	CRT with 5 FU	***Induction FOLFOX followed by CRT***	none	none	yes		
13	Male	64	Low	cT2N0	no mets	CRT with Capecitabine	no	Yes, 2.5 years	none	yes		Salvage surgery scheduled
14	Female	48	Low	cT3N1	no mets	CRT with Capecitabine	***Induction FOLFOX followed by CRT***	none	none	yes		
15	Male	82	Middle	cT2N0	no mets	CRT with 5 FU	no	none	none	yes		
16	Male	71	Low	cT2N0	no mets	CRT with Capecitabine	no	none	none	yes		
17	Male	60	Low	cT3N1	no mets	CRT with Capecitabine	***Induction FOLFOX followed by CRT***	none	none	yes		
18	Female	55	Middle	cT3N0	no mets	CRT with 5 FU	Consolidation chemo with FOLFOX (8 cycles)	none	none	yes		
19	Female	49	Low	cT3N1	no mets	CRT with 5 FU	Consolidation chemo with FOLFOX (8 cycles)	none	none	yes		
20	Male	70	Low	cT3N1	no mets	CRT with Capecitabine	Consolidation chemo with CAPOX (1 cycle)	yes	Liver + local, 13 months	yes		Salvage APR and Liver resection followed by 5-FU and Bevacizumab
21	Male	91	Low	cT3N1	no mets	CRT with 5 FU	no	none	none	yes		
22	Male	54	Low	cT3N2	no mets	CRT with Capecitabine	***Induction FOLFOX followed by CRT***	none	Isolated aortocaval node, 3 years	yes	yes	Additional chemotherapy and SBRT
23	Female	94	Low	cT3N0	no mets	CRT with 5 FU	no	none	none	no	no	Deceased due to other causes
24	Male	76	Middle	cT3N0	no mets	CRT with 5-FU	no	none	Liver, 9 months	yes		FOLFOX and Bevacizumab followed by liver resection
25	Male	66	Middle	cT3N0	no mets	CRT with Capecitabine	***Induction FOLFOX followed by CRT***	none	none	yes		
26	Male	76	Low	cT3N1	no mets	CRT with Capecitabine	***Induction FOLFOX followed by CRT***	none	none	yes		
27	Female	47	Low	cT3N0	no mets	CRT with Capecitabine	***Induction FOLFOX followed by CRT***	none	none	yes		
28	Female	71	Low	cT3N1-2	no mets	CRT with Capecitabine	Consolidation chemo with FOLFOX (8 cycles)	none	none	yes		
29	Female	67	Low	cT3N0	no mets	CRT with Capecitabine	Consolidation chemo with FOLFOX (8 cycles)	none	none	yes		

Blue: Distant Recurrence
Red: Local Recurrence
Light Blue: Local+Distant recurrence

4. Discussion

NOM for rectal cancer has been reported in the medical literature for over 15 years [13]. The need for definitive surgery after neoadjuvant therapy was debated when non-operatively managed patients with cCRs were compared with patients that had pCRs after resection, and these initial reports showed no significant differences in short-term oncologic outcomes between these two groups [5].

In patients that receive neoadjuvant therapy, it is both important to standardize criteria to define cCR as well as methods for appropriate surveillance. There remains a concern regarding the natural history of locoregional recurrence in these patients, and their ability to be salvaged. In an effort to answer this question, Habr-Gama et al. performed a follow-up study looking at patients with initial cCRs after neoadjuvant therapy sustained for at least one year. Ninety-nine (27.4%) of the 361 patients with low rectal cancers treated with neoadjuvant therapy sustained a cCR after a year of follow-up. Overall, there were 13 recurrences: 5 local recurrences that were managed with surgery or brachytherapy, 7 systemic recurrences, and 1 combined local/systemic recurrence. There were no *pelvic* recurrences that would have precluded salvage surgery. Distant recurrences without tumor regrowth are also a potential concern with non-operative management. A meta-analysis reported by Kong et al. demonstrated a 1.9% distant recurrence rate with the "watch and wait" strategy and no compromise of oncologic outcomes such as overall survival (OS) [12]. Several other series have also demonstrated equivalent OS and disease free survival (DFS) in patients who underwent radical surgery compared to patients managed non-operatively [6,8,14,15]. In our series, there were a total of 6 recurrences: 1 local, 4 distant metastatic and 1 combined local and distant. The combined local/distant was able to be successfully salvaged with surgery while the local recurrence is expected to be salvaged with surgery in the near future. Two of the 4 distant recurrences were able to be treated with a liver and lung resection together demonstrating that 67% patients with some variant of recurrence were salvaged with surgery. The isolated recurrence to an aortocaval node although not able to be treated with surgery is being treated with SBRT after additional chemotherapy.

The assessment of clinical response with concern for observer variability has also been controversial. Large series of patients reported by Habr-Gama followed with a NOM strategy have reportedly been followed by a single experienced colorectal surgeon [10]. In our series, one surgeon (SN) alone endoscopically followed these patients. Habr-Gama et al. reported in a 2014 study an initial cCR of 49%, increased from previously reported rates of only 27–30% partially due to a change in their criteria which re-classified patients with early local recurrence within twelve months as recurrences rather than incomplete responders. The group determined that differences in post-treatment assessment were potentially due to the learning curve associated with endoscopic assessment of these patients and changes in imaging modalities. Seventeen of the 90 "watch and wait" patients recurred locally within 1 year and 94% of these recurrences were successfully treated with surgery. Eleven patients recurred locally after 1 year and 91% of those patients were salvaged. A significant proportion of the patients who presented with late recurrences or local regrowth were found to have pT3/T4 disease [10]. This finding raises concern for the presence of viable malignant cells deeper within the rectal wall despite findings of cCR on mucosal examination. The presence of remnant nodal disease is also a concern after neoadjuvant therapy. In patients that have undergone resection, ypT0N + tumors are reported in 2–27% [16–19]. For these reasons, we feel it is essential that these patients undergo strict surveillance with MRI or ERUS.

Clinical assessment post-neoadjuvant therapy remains challenging because direct visual evaluation of tumor response does not always correlate with pathologic response [20,21]. Currently, we do not have an accurate technique to predict pathologic complete response (pCR) in patients managed non-operatively. The two modalities that are used at present are endoscopy and various imaging modalities. Clinical assessment may be improved by increased experience of the individual performing the endoscopy and improvements in radiographic imaging techniques [10,22]. Both diffusion weighted MRI and PET/CT have been shown to improve accuracy of predicting pCR after neoadjuvant therapy but there is a paucity of data for the use of these modalities [23,24]. Currently, the Magnetic Resonance Tumour Regression Grade as Biomarker for Stratified Management of Rectal Cancer Patients (TRIGGER Trial) is accruing patients in attempts to improve radiographic assessment [25]. By establishing an improved and accurate modality to predict pCR with patients that have a cCR, patient selection

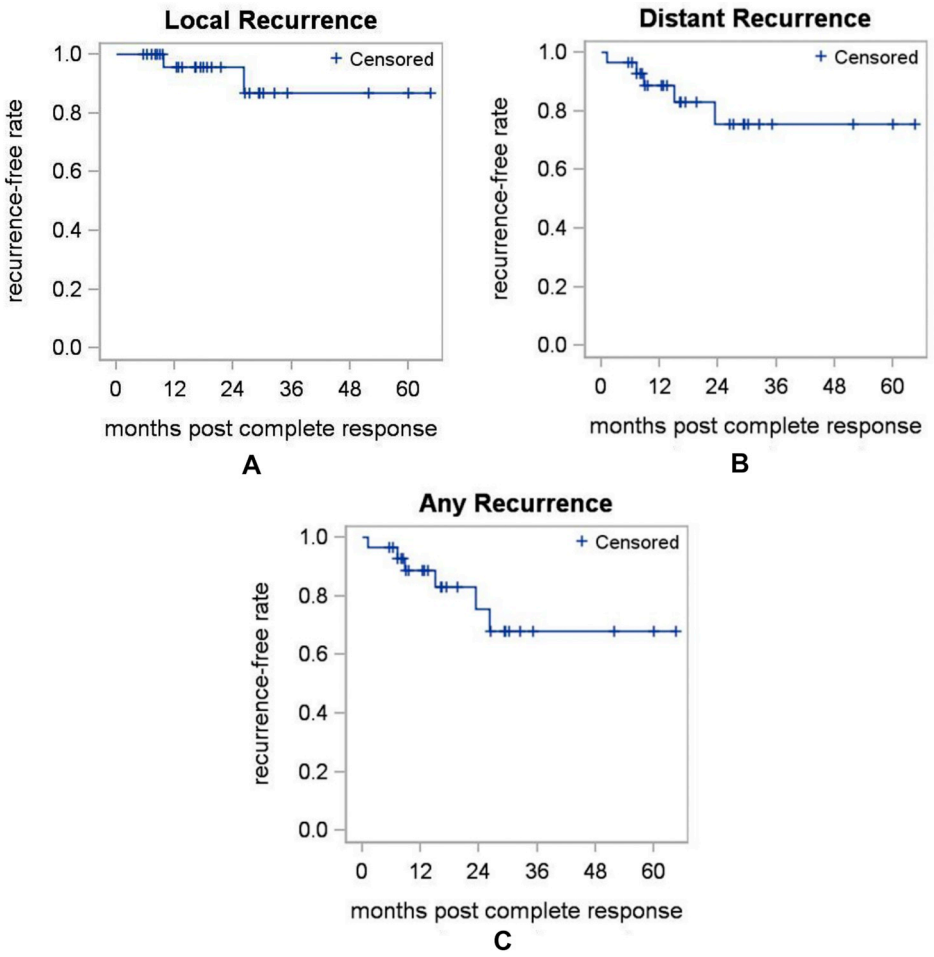

Fig. 1. a. Local recurrence-free survival. b. Distant recurrence-free survival. c. Any recurrence-free survival.

Table 3
Local, distant and any recurrence survival curves for rectal cancer after initial complete clinical responses to neoadjuvant therapy.

	1-yr Rate (95% CI)	3-yr Rate (95% CI)	Median Time (95% CI)	Median Follow-up (Range)	Sample
LOCAL	0.95 (0.72, 0.99)	0.87 (0.54, 0.97)	NR (NR, NR)		E = 2 C = 27 T = 29
DISTANT	0.89 (0.69, 0.96)	0.76 (0.49, 0.90)	NR (23.3, NR)		E = 5 C = 24 T = 29
Any Recurrence	0.89 (0.69, 0.96)	0.68 (0.40, 0.85)	NR (23.3, NR)	27.6 months (5.5, 64.5)	E = 6 C = 23 T = 29

for non-operative management could be improved.

5. Limitations

The limitations of our study include a group with various treatment strategies and relatively short-term follow-up. Based on some of the benefits of total neoadjuvant therapy, our group has now been offering this approach to the majority of our patients with locally advanced rectal cancer. A significant portion of the patients underwent either induction or consolidation chemotherapy regimens prior to consideration of non-operative management. For newly diagnosed patients, we typically start with systemic therapy, followed by CRT. Some patients we first evaluated after being treated with chemoradiation at an outside facility. These patients were then scoped, and offered consolidation chemotherapy. There is currently a phase II trial multi-center trial evaluating chemoradiation plus induction or consolidation chemotherapy and total mesorectal excision or NOM in patients with locally advanced rectal cancer [26]. We are awaiting the results of this trial to determine which neoadjuvant strategies can optimize response rates and potential NOM.

We generally recommend chemotherapy after neoadjuvant CRT in patients that are managed non-operatively if the patient is medically fit enough to tolerate it. Based on the pre-operative staging of our patients and roughly double the rates of clinical nodal disease in Habr-Gama's reports, we feel that our use of chemotherapy either before or after CRT is prudent but it is not without controversy. Kong et al. reported in a meta-analyses demonstrating equivalent distant and local recurrence rate between the non-operative and immediate surgery groups that received consolidation chemotherapy regimens [12]. Other series have also confirmed no differences in overall survival, disease-free survival, and distant recurrence with consolidation chemotherapy [6,14,27]. Fifteen of the 31 patients (48.4%) in our study had pre-treatment positive nodal disease that puts them at higher risk of developing both local and distant disease. This rate of nodal disease was higher than other large trials by more than two-fold [5,7,10].

6. Conclusion

This is one of the largest single institution U.S. series evaluating patients undergoing total neoadjuvant therapy and NOM. Although non-operative management is currently not considered the standard of care, it is our group's decision to offer it based on previously published retrospective data. Tailoring treatment decisions based on patient's goals cannot be more relevant in the current management of locally advanced rectal cancer. In the era of patient-centered medicine, we feel that the patient should get to choose what the best treatment is for them. For some patients, it is the maintenance of intestinal continuity and stoma-free life; for others, it is the best chance of a cure no matter the risks. It is clear that some patients with rectal cancer can be cured without surgery. Based on preliminary data, it seems the majority of patients that experience a rectal cancer recurrence after a cCR are salvageable with surgical intervention without compromising oncologic outcomes. Further research is needed to evaluate long term outcomes, as well as to define optimal treatment strategies for patient selection, neoadjuvant treatment and post-therapy surveillance.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2018.11.012.

References

[1] R.L. Siegel, K.D. Miller, S.A. Fedewa, et al., Colorectal cancer statistics, CA A Cancer J. Clin. 67 (2017) 177–193 2017.
[2] R.J. Heald, E.M. Husband, R.D. Ryall, The mesorectum in rectal cancer surgery–the clue to pelvic recurrence? Br. J. Surg. 69 (1982) 613–616.
[3] B.C. Paun, S. Cassie, A.R. MacLean, et al., Postoperative complications following surgery for rectal cancer, Ann. Surg. 251 (2010) 807–818.
[4] C.Y. Kang, W.J. Halabi, O.O. Chaudhry, et al., Risk factors for anastomotic leakage after anterior resection for rectal cancer, JAMA Surg. 148 (2013) 65–71.
[5] A. Habr-Gama, R.O. Perez, W. Nadalin, et al., Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results, Ann. Surg. 240 (2004) 711–717 discussion 717-718.
[6] M. Maas, R.G. Beets-Tan, D.M. Lambregts, et al., Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer, J. Clin. Oncol. 29 (2011) 4633–4640.
[7] A. Habr-Gama, R.O. Perez, I. Proscurshim, et al., Patterns of failure and survival for nonoperative treatment of stage c0 distal rectal cancer following neoadjuvant chemoradiation therapy, J. Gastrointest. Surg. 10 (2006) 1319–1328 discussion 1328-1319.
[8] A.G. Renehan, L. Malcomson, R. Emsley, et al., Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis, Lancet Oncol. 17 (2016) 174–183.
[9] A.L. Appelt, J. Ploen, H. Harling, et al., High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study, Lancet Oncol. 16 (2015) 919–927.
[10] A. Habr-Gama, J. Gama-Rodrigues, G.P. Sao Juliao, et al., Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control, Int. J. Radiat. Oncol. Biol. Phys. 88 (2014) 822–828.
[11] G. Nessar, Organ preservation in rectal cancer patients following complete clinical response to neoadjuvant chemoradiotherapy: long-term results in three patients, Ulus Cerrahi Derg. 30 (2014) 219–221.
[12] J.C. Kong, G.R. Guerra, S.K. Warrier, et al., Outcome and salvage surgery following "watch and wait" for rectal cancer after neoadjuvant therapy: a systematic review, Dis. Colon Rectum 60 (2017) 335–345.
[13] W.T. Nakagawa, B.M. Rossi, O.F.F. de, et al., Chemoradiation instead of surgery to treat mid and low rectal tumors: is it safe? Ann. Surg. Oncol. 9 (2002) 568–573.
[14] J.D. Smith, J.A. Ruby, K.A. Goodman, et al., Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy, Ann. Surg. 256 (2012) 965–972.
[15] C.L. Lai, M.J. Lai, C.C. Wu, et al., Rectal cancer with complete clinical response after neoadjuvant chemoradiotherapy, surgery, or "watch and wait, Int. J. Colorectal Dis. 31 (2016) 413–419.
[16] I. Bedrosian, M.A. Rodriguez-Bigas, B. Feig, et al., Predicting the node-negative mesorectum after preoperative chemoradiation for locally advanced rectal carcinoma, J. Gastrointest. Surg. 8 (2004) 56–62 discussion 62-53.
[17] E.D. Mignanelli, L.F. de Campos-Lobato, L. Stocchi, et al., Downstaging after chemoradiotherapy for locally advanced rectal cancer: is there more (tumor) than meets the eye? Dis. Colon Rectum 53 (2010) 251–256.
[18] T.E. Read, J.E. Andujar, P.F. Caushaj, et al., Neoadjuvant therapy for rectal cancer: histologic response of the primary tumor predicts nodal status, Dis. Colon Rectum 47 (2004) 825–831.
[19] J. Seong, J.H. Cho, N.K. Kim, et al., Preoperative chemoradiotherapy with oral doxifluridine plus low-dose oral leucovorin in unresectable primary rectal cancer, Int. J. Radiat. Oncol. Biol. Phys. 50 (2001) 435–439.
[20] F.M. Smith, H. Wiland, A. Mace, et al., Clinical criteria underestimate complete pathological response in rectal cancer treated with neoadjuvant chemoradiotherapy, Dis. Colon Rectum 57 (2014) 311–315.
[21] J.E. Ryan, S.K. Warrier, A.C. Lynch, A.G. Heriot, Assessing pathological complete response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer: a systematic review, Colorectal Dis. 17 (2015) 849–861.
[22] A. Habr-Gama, R. Perez, I. Proscurshim, J. Gama-Rodrigues, Complete clinical response after neoadjuvant chemoradiation for distal rectal cancer, Surg. Oncol. Clin. N. Am. 19 (2010) 829–845.
[23] M. Maas, D.M. Lambregts, P.J. Nelemans, et al., Assessment of clinical complete response after chemoradiation for rectal cancer with digital rectal examination, endoscopy, and MRI: selection for organ-saving treatment, Ann. Surg. Oncol. 22 (2015) 3873–3880.
[24] R.O. Perez, A. Habr-Gama, J. Gama-Rodrigues, et al., Accuracy of positron emission tomography/computed tomography and clinical assessment in the detection of complete rectal tumor regression after neoadjuvant chemoradiation: long-term results of a prospective trial (National Clinical Trial 00254683), Cancer 118 (2012) 3501–3511.
[25] https://clinicaltrials.gov/ct2/show/NCT02704520.
[26] https://clinicaltrials.gov/ct2/show/NCT02008656?term=NONOPERATIVE+RECTAL+CANCER&cntry=US&rank=1.
[27] R.K. Smith, R.D. Fry, N.N. Mahmoud, E.C. Paulson, Surveillance after neoadjuvant therapy in advanced rectal cancer with complete clinical response can have comparable outcomes to total mesorectal excision, Int. J. Colorectal Dis. 30 (2015) 769–774.