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REVIEW

Risk factors for local recurrence following neoadjuvant chemoradiotherapy for rectal cancers

Jia-Yuan Peng, Zhong-Nan Li, Yu Wang

Jia-Yuan Peng, Zhong-Nan Li, Yu Wang, Department of Surgery, Shanghai Sixth People's Hospital, Shanghai Jiao Tong University, Shanghai 200233, China
Author contributions: Peng JY and Li ZN contributed equally to this work; Peng JY reviewed the literature and wrote the article; Li ZN contributed to the analysis and interpretation of the data; Wang Y designed the review and revised the article; all authors have read and approved the final version to be published.
Correspondence to: Yu Wang, Professor, Department of Surgery, Shanghai Sixth People's Hospital, Shanghai Jiao Tong University, 600 Yishan Road, Shanghai 200233, China. wangyu11122@126.com
Telephone: +86-21-64361349 Fax: +86-21-64368920
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Abstract

Local recurrence (LR) has an adverse impact on rectal cancer treatment. Neoadjuvant chemoradiotherapy (nCRT) is increasingly administered to patients with progressive cancers to improve the prognosis. However, LR still remains a problem and its pattern can alter. Correspondingly, new risk factors have emerged in the context of nCRT in addition to the traditional risk factors in patients receiving non-neoadjuvant therapies. These risk factors are decisive when reviewing treatment options. This review aims to elucidate the distinctive risk factors related to LR of rectal cancers in patients receiving nCRT and to clarify their clinical significance. A search was conducted on PubMed to identify original studies investigating patients with rectal cancer receiving nCRT. Outcomes of interest, especially potential risk factors for LR in patients with nCRT, were then analyzed. The clinical importance of these risk factors is discussed. Remnant cancer cells, lymph-nodes and tumor response were found to be major risk factors. Remnant cancer cells decide the status of resection margins. Local excision following nCRT is promising in ypT0-1N0M0 cases. Dissection of lateral lymph nodes should be considered in advanced low-lying cancers. Although better tumor response resulted in a relatively lower recurrence rate, the evidence available is insufficient to justify a non-operative approach in clinical complete responders to nCRT. LR cannot be totally avoided by current multidisciplinary approaches. The related risk factors resulting from nCRT should be considered when making decisions regarding treatment selection.

Key words: Local recurrence; Rectal cancer; Neoadjuvant chemoradiotherapy

Core tip: This review identifies the distinctive risk factors associated with local recurrence (LR) in patients with rectal cancer receiving neoadjuvant therapy. These factors are different from the traditional risk factors seen in patients treated with surgery and/or adjuvant therapy alone. The clinical significance of these risk factors is clarified in detail. To our knowledge, no reviews concerning this topic have been published. The present manuscript might help to understand the origin of LR following neoadjuvant chemoradiotherapy and may receive attention from investigators devoted to improving the prognosis of rectal cancer.

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INTRODUCTION

Local recurrence (LR) is a major problem and threatens the prognosis of rectal cancer patients. For locally pro-

gressive tumors, LR can not be prevented just by improving surgical techniques. Therefore, preoperative, also known as neoadjuvant, therapy has been advocated due to its ability to down-stage tumors and thus increase resectability. Multidisciplinary neoadjuvant approaches have been proven to effectively control LR[1,2] and improve overall survival[3,4]. However, LR still occurs[5,6] and its pattern can change[7,8] with regard to time and location. For example, the time from operation to LR is prolonged[9]. Most importantly, neoadjuvant therapy and its downsizing effects on tumors have resulted in the emergence of some LR-associated risk factors unlike those related with only surgery plus adjuvant chemoradiotherapy, such as vascular invasion or tumor differentiation[8,10]. These distinctive risk factors, consisting of isolated remnant cancer cells and tumor response to neoadjuvant chemoradiotherapy (nCRT), have been reported to be associated with the prognosis of patients[11]. Therefore, determination of the characteristics of these factors and their clinical significance would provide very helpful data for clinical practice.

The aim of the present review was to characterize the risk factors in patients receiving neoadjuvant therapy, mainly nCRT. Moreover, the clinical implications of these risk factors in treatment decision-making following nCRT were also explored.

SEARCHING STRATEGIES AND SELECTING CRITERIA

A systematic review was performed in order to explore potential risk factors for LR following nCRT. A literature search was performed in PubMed and EMBASE databases for English-language papers published over the last 10 years, with outcome data limited to humans. The search terms used included "rectal cancer" or "rectal neoplasm"; "neoadjuvant" or "preoperative"; "radiotherapy" or "chemotherapy" or "chemoradiotherapy"; "recurrence" or "local recurrence" or "local control" or "local relapse" or "local failure" or "prognosis".

The criteria for including potential studies in the systematic review were: (1) randomized clinical trials (RCTs) or cohort studies investigating patients with rectal cancer receiving nCRT; (2) retrospective studies of LR in patients with rectal cancer who were treated with nCRT; and (3) studies evaluating parameters (risk factors) that may influence the outcome in terms of LR in patients with rectal cancer who were treated with nCRT. Articles that did not show LR or investigate the causes of LR were excluded. Furthermore, abstract-only publications and chapters from books were excluded. When the same series of patients were reported by the same authors in different articles, only the series with the longest follow-up was included in the review.

Two reviewers independently reviewed each article, and discrepancies were resolved by discussion and consensus. All data were extracted from the main text, tables, and figures of the articles. Traditional risk factors such as differentiation, vascular invasion, TNM staging and circumferential resection margin status were excluded. Risk factors related to the downsizing effect of nCRT were included.

Analysis of the data from the included studies was carried out. Descriptive statistics (simple counts, means, and medians) were either directly derived from the article or calculated based on the data presented in the article, and used to report studies, patients, and treatment-level data. Outcomes of interest, especially potential risk factors for LR in patients who received nCRT were synthesized by pooling relevant data, and then analyzed. Due to high heterogeneity among the studies and lack of RCTs, a meta-analysis was not deemed appropriate.

PATTERNS OF LR FOLLOWING nCRT

Time and location of LR

To better understand the risk factors, a deep insight into the patterns of LR is required. The patterns of LR can be described by two aspects, namely timing and location. The first aspect is the time interval to development of LR. Habr-Gama *et al*[9] found that the mean recurrence interval was 52 mo (18-79 mo) in 6 cases with sustained complete clinical response to nCRT. However, Coco *et al*[6] reported that the time to development of LR was longer than 5 years in approximately one third of cases treated with nCRT (4 of 14 cases). Similar results were observed in studies[12,13], in which only neoadjuvant radiotherapy (nRT) was administered. However, in a study which included patients receiving surgery alone or associated with postoperative chemoradiotherapy (pCRT) with an average follow-up of 10 years, LR occurred in 72% of patients within 18 mo of surgery[14]. These data suggest that neoadjuvant therapy may have an ongoing impact, different from that of pCRT, on the natural history of rectal cancer. This may be the reason why a better response can be induced by nCRT over time[15,16].

The second pattern is the subtle alteration concerning subsites of LR. It has been shown that the incidence of anastomotic recurrence is declining[12,17]. The two most common sites of LR in nCRT cases are the lower pelvis (56%) and presacral region (22%)[18,19]. Syk *et al*[20] indicated that the majority of LRs in patients receiving nRT were located anatomically below the S1-S2 interspace. The higher frequency of LR within the presacral area in patients undergoing nRT may be explained by the unique anatomical locations of the mesorectum and lateral lymph nodes (LLNs). The mesorectum is defined as the fatty and fibrous tissues surrounding the rectum. Most mesorectal tissues are located at the dorsal side of the rectum and include lymphatic and vascular vessels to which cancer may disseminate. Furthermore, a recent anatomical study revealed the presence of an alternative lymphatic drainage pathway from mesorectal LNs to LLNs[21] using three-dimensional reconstruction and histological section. This connection may provide a pathway for the cancer cells to spread or escape and LLNs may

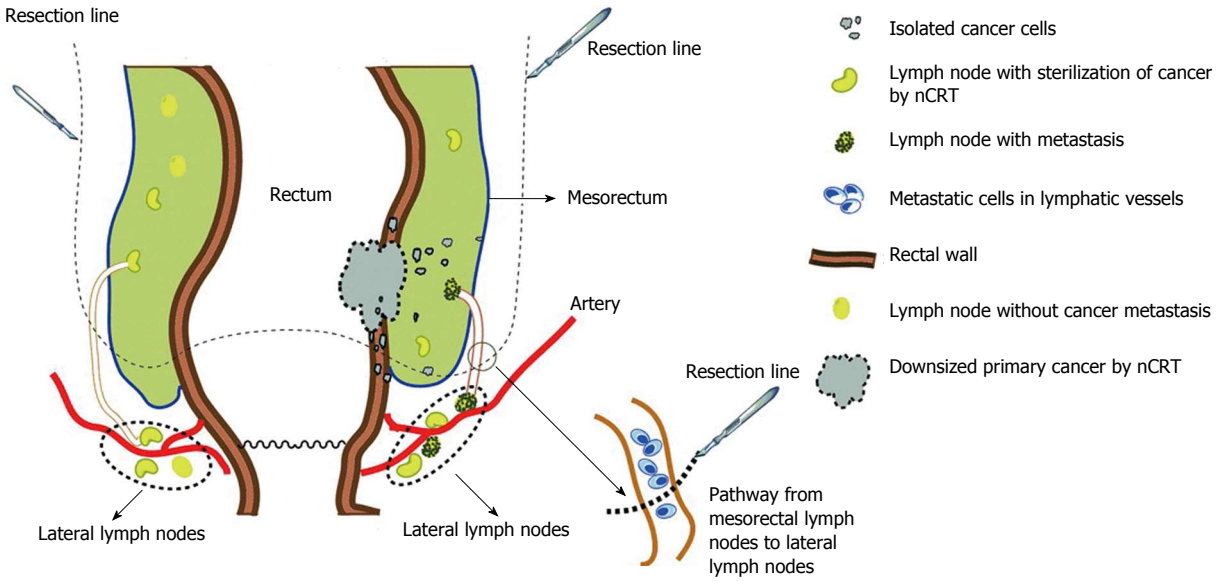

Figure 1 A diagram of risk factors for local recurrence in cases treated with neoadjuvant chemoradiotherapy. Resection line marks the resection range of a standard total mesorectum resection. nCRT: Neoadjuvant chemoradiotherapy.

serve as a harbor for these cells[22,23]. Some isolated cancer cells in the mesorectum or lymphatic tissues (see "Isolated tumor cells") serve as seeds for LR following nCRT. These cells are inhibited, but not killed, by nRT and rest in the G0 phase[24]. During surgery, cells may be spilled and implanted in the lower pelvis and presacral region resulting in LR.

We hypothesize that the seeds of LR may be the cancer cells at the margin of the mesorectum or within the lymphatic pathway from the mesorectum to LLNs. During a standard total mesorectum resection (TME), these cells may "leak" following complete resection of the mesorectum, implant in the presacral space due to the force of gravity and trigger subsequent LR (Figure 1). This hypothesis may be further confirmed if the tumor cells can be separated from post-operative lymph fluid drainage.

Clinical importance of follow-up

Understanding the altered LR patterns in patients with different neoadjuvant and intraoperative therapies has practical implications. On the one hand, delayed LR occurs in patients receiving nCRT, and thus, the standard 5-year follow-up currently recommended by the European Society for Medical Oncology[25] should be extended to at least 7-8 years and intensified monitoring is required in selected cases[26]. In addition, if delayed LR is expected to occur in a proportion of patients, the observational period in prospective and randomized trials[4,27] should be prolonged in order to draw more definitive conclusions. On the other hand, attention should be paid to common regions involved in LR in patients receiving neoadjuvant therapies which may help us accurately select the area at high risk for radiotherapy and avoid unnecessary irradiation.

ISOLATED REMNANT CANCER CELLS

As mentioned above, nCRT may be "suppressive" rather than "destructive" for a certain proportion of cancer cells. Thus, the surviving cells, if not removed by surgery, may restore their viability and evolve into seed cells for LR (Figure 1). These seed cells can be divided into two groups, extranodal and intranodal seed cells, according to their relationship with lymph nodes (LNs). Furthermore, two major types of LR derived from extranodal seed cells, tumor budding (inside the bowel wall) and mesorectal microfoci (MMF), have been reported, according to their locations.

TUMOR BUDDING

Relationship with LR

Tumor budding is described as a subset of isolated cancer cells located at the invasive front and extending from the neoplastic gland structures to the adjacent stroma[28]. Tumor budding has been reported to be an independent factor predicting prognosis[29,30]. Research on nCRT cases has shown that tumor budding is always described as isolated or small clusters of remnant cancer cells resulting from tumor regression. A control-case study[24] showed that nRT increased the frequency of budding cells compared with surgery without nRT (mean 54 *vs* 38, $P = 0.03$). These cells are always surrounded by fibrosis or an inflammatory reaction induced by nCRT. NCRT-induced tumor budding can be classified into two grades: high grade (clusters of budding cells easily observed by pathological examination) and low grade (minimal or isolated budding barely detected by pathological examination). According to Gavioli *et al*[31] study of 139 patients with nCRT, LR did not appear in the low grade budding group, while 8.8% of the high grade budding patients developed LR. In a more recent study, patients with low grade budding also had better 5-year disease-free survival than those with high grade budding (87.5% *vs* 55.6%, $P < 0.0001$).

Table 1 Intramural spreading distance after neoadjuvant therapy

Ref.	No. of patients	Neoadjuvant therapy regimen		Intramural spreading distance		
		Radiotherapy (Gy)	Chemotherapy	0-5 mm	6-10 mm	> 10 mm
Chmielik *et al*[32]	106	5 × 5	None	93	9	4
Chmielik *et al*[32]	86	50.4	5-Fu + LV	78	8	0
Mezhir *et al*[37]	20	50.4	5-Fu + LV	12	7	1
Guillem *et al*[36]	109	50.4	5-Fu + LV	108	1	0

5-Fu: 5-fluorouracil; LV: Leucovorin.

Clinical significance: decide the status of distal resection margin

It has been shown that the distal intramural spread of tumor budding is discontinuous in 57% of patients receiving nCRT[32]. The nature of this discontinuity is of special clinical importance; the supposed "clean" distal resection margin (DRM) in sphincter-sparing resection may not necessarily be free of cancer cells and longer a DRM may be required in a proportion of patients due to the possible existence of tumor budding. Thus, the focus is now "How far does tumor budding go?" Two studies demonstrated that DRMs less than 10 mm did not compromise LR[33,34]. In contrast, a study with a longer follow-up (5.6 years) demonstrated that a DRM less than 8 mm was associated with increased LR[35]. Why was there discrepancy between these two studies? First, the average period of follow-up may have had an influence. The follow-up time in these two studies may have been too short to draw definite conclusions (both were less than 36 mo). Second, the whole-mount section of the pathological examination was not used in these two studies, making the conclusion less convincing. Studies using whole-mount sections have shown that approximately 90% of patients receiving nCRT have a distal intramural extension of tumor budding within 5 mm, and 8% within 6-10 mm and less than 2% over 10 mm[32,36,37] (Table 1). Correspondingly, it has been suggested that the required length of the DRM should be shortened from 20 to 10 mm due to tumor remission induced by nCRT[36]. A DRM less than 10 mm is not yet justified for cases receiving nCRT based on current evidence. Therefore, following nCRT, the existence of budding cells is discontinuous and a supposed "negative" DRM less than 10 mm may not be a real negative margin for low-lying cancers.

MMF

Relationship with LR

Unlike tumor budding which is intramural, MMF, another risk factor for LR, is mesorectal. MMF is primarily defined as extranodal cancer deposits discontinuous with the primary tumor[38] in the mesorectum. The incidence of MMF is reported to be directly associated with the infiltrating depth of the primary tumor[38].

Ratto *et al*[39] specifically classified MMF into four major subtypes: endovascular (cancer deposits in blood vessels), endolymphatic (cancer deposits in lymphatic vessels but not in lymph nodes), perineural (cancer cell aggregates between the fasciculus and perineurium) and isolated (cancer deposits within the mesorectum, not a continuous extension from the main tumor mass). Clinically, MMF can be identified by careful pathological examination. Studies[39-41] have shown that MMF are detected in 13.8%-44.2% of cases after surgery despite downstaging induced by nCRT. Prabhudesai *et al*[38] reported that LR occurred in 17.2% (5/29) of patients with MMF and in 3.8% (1/26) of those without MMF, although the difference was not statistically significant.

Clinical significance: decide the status of circumferential resection margin and distal mesorectal margin

Similar to tumor budding, MMF may decide the status of the circumferential resection margin (CRM) and distal mesorectal margin (DMM) (Figure 2). However, no data are available regarding the appropriate CRM and DMM after nCRT. Should CRM and DMM be correspondingly shortened? Further pathological studies are required.

LYMPH NODES

Relationship with LR

Cancer cells harbored within LNs surrounding the rectum may serves as the seeds for LR. Although the nCRT-induced tumor regression does not necessarily parallel the sterilization of LNs metastasis, better tumor response may predict less LNs metastasis. Recent studies have proven that tumors at stage ypT0-1 correlate with a very low incidence of positive LN involvement[31,42-52] (Table 2). With regard to stage ypT2, LN involvement is present in about 20%-30% of cases[44,48].

Clinical significance: indication for local excision

With the belief that favorable tumor response may be equal to the disappearance of LNs metastasis, we propose that a proportion of pretreated T3 or T4 tumors might meet the requirements for local excision (LE). Several studies have shown that LR is not observed in ypT0 cases followed by LE, and the LR rate is around 3%-6% in ypT1 cases[53-60]. Moreover, the LR cases can be efficiently salvaged by subsequent radical dissection if early detection is achieved[54,61]. Therefore, LE is recommended by some authors for ypT0 or ypT1 cases due to its efficacy in local control which is equivalent to radical surgery[49,52,53,59,61-64]. Although these results are encouraging, the majority of the above-mentioned studies are retrospective and include small sample sizes. Thus, further

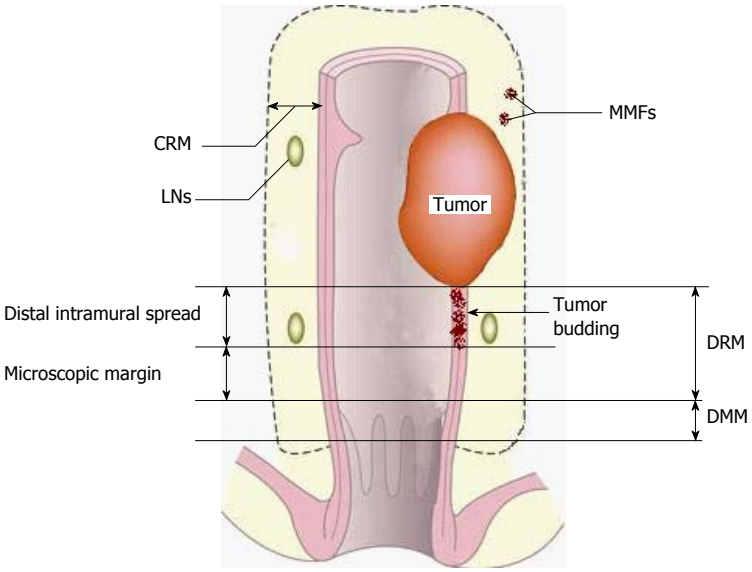

Figure 2 A diagram of resection margins of rectal cancer and their relationships with mesorectal microfoci and tumor budding. CRM: Circumferential resection margin; DRM: Distal resection margin. DMM: Distal mesorectal margin; LNs: Lymph nodes; MMF: Mesorectal microfoci.

Table 2 Association between ypT stage and ypN status *n* (%)

Ref.	No. of patients	Neoadjuvant therapy regimen		Time interval[1] (wk)	No. of patients with ypT0/T1	
		Radiotherapy (Gy)	Chemotherapy		ypN+/ypT0-1	ypN+/ypT2-4
Zmora *et al*[42]	109	45-50.4	5-Fu	6	4/33 (12.1)	30/61 (49.2)
Read *et al*[43]	644	20-45	5-Fu	NS	3/87 (3.4)	217/557 (39.0)
Bujko *et al*[44]	147	5 × 5		1	0/4 (0.0)	69/138 (50.0)
Bujko *et al*[44]	138	50.4	5-Fu	4-6	2/33 (6.1)	41/101 (40.6)
Pucciarelli *et al*[45]	235	45-50.4	5-Fu	6-8	3/69 (4.3)	45/166 (27.1)
Tulchinsky *et al*[46]	101	45	5-Fu	5-7	1/22 (4.5)	29/75 (38.7)
Habr-Gama *et al*[47]	401	50.4	5-Fu	8	3/25 (10.7)	75/224 (33.5)
Stipa *et al*[48]	187	50.4	5-Fu	NS	3/44 (6.8)	48/143 (33.6)
Kundel *et al*[49]	320	45	5-Fu	4-8	3/69 (4.3)	49/222 (22.1)
Gavioli *et al*[31]	139	50	5-Fu	4	2/34 (5.9)	38/105 (36.2)
Kim *et al*[50]	282	45	5-Fu	4-8	2/58 (3.4)	85/224 (37.9)
Lindebjerg *et al*[51]	135	60	5-Fu	8	8/47 (17.0)	32/88 (36.4)
Coco *et al*[52]	271	NS	NS	NS	3/71 (4.2)	70/200 (35.0)
Total	3109				37/596 (6.2)	828/2304 (35.9)

[1]Time interval refers to the time from the end of neoadjuvant therapy to subsequent operation. NS: Not specified; 5-Fu: 5-fluorouracil.

prospective, population-based and multi-center investigations are required to confirm these results.

With regard to ypT2 stage, 63% (53/88) of patients with ypT2 are reported to have at least one unfavorable pathological feature in addition to LNs metastases (vascular or perineural invasion, mucinous type and tumor size > 3 cm) for LE[65]. Perez *et al*[66] reported that the LR rate in patients with ypT2 who underwent LE was 9% (8/88) after nCRT. In cases with ypT3N0 or ypT4N0, the rate was up to 25% (14/25), including 14.7% (n = 8) systemic and 10.3% (n = 6) local relapse despite the absence of LNs micro-metastasis[66]. These findings indicate that ypT2-4 may have more residual cancer cells than detected and these tumor stages are not suitable for LE under the current nCRT regimen.

LATERAL LYMPH NODES

Relationship with LR

LLNs are a particular type of lymph nodes and dissection of LLNs is not included during regular TME. The incidence of LLN involvement varies from 7.7% to 20% in low and middle rectal cancer[67-69]. There is evidence to suggest that TME even with nCRT cannot completely remove remnant cancer cells in LLNs (Figure 1), especially in advanced tumors[45,70,71]. Kim *et al*[72] reported that 9 (7.9%) of 366 patients developed LR after nCRT and TME during a mean follow-up of 5 years, and lateral pelvic recurrence accounted for most (n = 24, 82.7%) of these cases. Patients with positive LLNs had a higher risk of lateral pelvic recurrence, compared with those with negative LLNs (LR rate: 26.6% *vs* 2.3%). Kusters *et al*[73] demonstrated that bilateral lateral lymph node dissection (LLND) generally resulted in better local control than unilateral LLND (LR rate: 15.4% *vs* 8.3%) in patients with advanced cancers after nCRT. When positive LLNs were detected preoperatively, the difference between unilateral and bilateral LLND was still significant (LR rate: 32.8% *vs* 14.2%). Furthermore, LR was detected on the contralateral side in a proportion of patients who

Table 3 Relationship between tumor response and local recurrence rate *n* (%)

Ref.	No. of patients	Neoadjuvant therapy regimen		No. of LR	
		Radiotherapy (Gy)	Chemotherapy	pCR LR/total	Non-pCR LR/total
Gavioli *et al*[31]	139	50	5-Fu	0/25 (0.0)	8/114 (7.0)
Stipa *et al*[57]	200	50	5-Fu	0/60 (0.0)	6/140 (4.3)
Hughes *et al*[71]	130	45	5-Fu	0/23 (0.0)	23/107 (17.7)
Kim *et al*[82]	114	50.4	5-Fu	0/10 (0.0)	17/104 (16.3)
Kuo *et al*[83]	248	50	5-Fu	2/36 (5.6)	66/212 (31.1)
Chan *et al*[84]	128	50	5-Fu	0/32 (0.0)	24/96 (18.4)
García-Aguilar *et al*[86]	168	40-65	5-Fu	0/21 (0.0)	7/147 (5)
Wheeler *et al*[87]	63	45-50	5-Fu	1/29 (3.4)	8/34 (23.5)
Theodoropoulos *et al*[88]	88	45	5-Fu	0/16 (0.0)	3/72 (4.2)
Total	1278			3/252 (1.2)	162/1026 (15.8)

LR: Local recurrence; pCR: Pathologic complete remission; 5-Fu: 5-fluorouracil.

underwent unilateral lymph node dissection. These data indicate that positive LLNs are a vital risk factor causing pelvic recurrence even after nCRT.

Clinical significance: application of LLND

There is controversy between Western and Japanese researchers concerning the application of LLND. Western researchers believe that nCRT plus TME may have a comparable outcome to that of LLND[74]. Moreover, resection of LLNs may result in injury to pelvic nerves. Thus, they recommend nCRT plus TME, not LLND. However, Japanese researchers indicate that LLND has a comparable outcome to that of nCRT plus standard TME regarding local control and the incidence of complications[75]. Thus, they recommend LLND. In our opinion, LLNs status is reflective of overall mesenteric LNs status and LLNs positivity may represent the poor response of rectal cancer to nCRT. LLND should be undertaken in selected patients, *e.g.*, those with tumor below the peritoneal reflection and poor tumor response. In addition, laparoscopic technology has unique advantages over laparotomy in terms of decreasing morbidity following LLND due to its high-definition close view in nerve-sparing.

TUMOR RESPONSES

Relationship with LR

A better tumor response may predict a more favorable prognosis for patients with advanced rectal cancer[76]. The response to neoadjuvant therapy includes remission in both primary tumor volume and lymphatic or vascular metastasis. Pathologic complete response (pCR) is defined as both ypT0 and ypN0, and the pCR rates range from around 10% to 30% in patients who underwent nCRT[77-80]. The final pathologic stage after nCRT and radical surgery is considered a vital factor in predicting LR. According to Mandard's Tumor Regression Grade (TRG) criteria[81], patients achieving a significant tumor remission (TRG1-3) displayed a relatively lower LR rate[71,82-87] compared with the non-downstaging group (TRG4-5). This figure decreased to 0%[31,71,82,86,88] (Table 3) in the pCR group. The reason for this may be that a pCR suggests a more favorable biological behavior and increases the chances of R0 resection. Moreover, complete regression of the primary cancer is paralleled with the disappearance of remnant cancer cells either in the mesorectum or lymph nodes[39].

Clinical significance: non-operative management

It has been shown that in patients with pCR, no residual cancer is found in resected specimens. This raises the question as to whether immediate radical surgery following nCRT is necessary, or, whether "watch and wait" is an appropriate strategy for these selected patients. Since pathological response can be judged only after tumor resection, a substitute parameter, clinical complete response (cCR), has been used to preoperatively screen potentially suitable patients[9,89]. A single-center study revealed that in patients treated with chemotherapy without surgery, only 5% of cCR cases (5 of 99) developed LR[9], whereas another study found that 8 of 10 patients had LR[90]. How do we explain such a big discrepancy? Actually, the critical premise for the "watch and wait" approach is to correctly identify the "real" suitable responders. A long-term persistent cCR may be a better representative of pCR. Only patients with sustained cCR for at least 12 mo were submitted to non-operative management in the study by Habr-Gama *et al*[9]. In contrast, the majority (75%) of patients with a short-term cCR (6-12 wk) were reported to have microscopic remnant cancers[70], at high risk of LR if subjected to "watch and wait". In addition, accuracy of staging in cases pretreated with nCRT is controversial. The absence of palpable tumors is not reliable evidence, nor is an invisible tumor on imaging methods, including transrectal ultrasonography, CT and MRI. Therefore, the overall attitude toward non-operative management remains critical and cautious, although the results from Habr-Gama *et al*[9,91] are promising. In our opinion, only selected cCR patients may undergo close observation without immediate radical surgery.

A CONTEMPORARY LOOK AT SURGERY-ASSOCIATED FACTORS

With the adoption of TME, LR and survival have im-

proved significantly in patients with rectal cancer, especially in those receiving anterior resection (AR)[92]. In comparison, abdominoperineal resection (APR) is reported to be related to a higher LR rate and poorer prognosis[93,94]. A possible explanation for the inferior outcome after APR is that surgeons often encounter more difficulties when resecting lower-lying tumors within a narrow pelvis[93]. Moreover, for those receiving nCRT, the appropriate surgical plane may be difficult to recognize due to tissue edema and fibrosis. These factors together may lead to inadequate excision of the mesorectum or of the tumor itself. In addition, the incidence of inadvertent intra-operative rectal perforation and post-operative anastomotic leak may increase, resulting in a higher LR rate[95-97].

With regard to AR, there is a legitimate concern about implanting exfoliated tumors cells when using circular staples. Despite the feasibility of low colorectal anastomosis, staples may also lead to implantation of viable tumor cells lying freely in the bowel lumen during staple firing[98,99]. That may also explain the mechanism of anastomotic recurrence in patients receiving nCRT (see Patterns of LR Following nCRT), who were expecting that tumor regression may translate to final sphincter-sparing surgery. Some authors[100,101] recommend intra-operative washout to eliminate exfoliated cancer cells because it is relatively risk-free and adds little to the operative trauma. However, it is difficult for surgeons to accomplish rectal washout in laparoscopic AR, as frequent laparoscopic manipulation probably increases tumor exfoliation, making wash-out even more crucial. Therefore, specific equipment or tools need to be designed to overcome the technical problems of laparoscopic rectal wash-out.

CONCLUSION

nCRT can downsize rectal cancer and facilitate subsequent radical resection. However, the impact of nCRT on downstaging of rectal cancer may also result in an altered pattern of LR and several distinctive risk factors for LR. These distinctive risk factors and altered patterns of LR are of clinical importance because they are decisive in treatment selection and follow-up. In future studies, we should not only identify but also improve our multidisciplinary approaches to minimize these factors.

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