Original Article

Short-term Outcome of "Watch and Wait" for Rectal Cancer with Clinical Complete Response after Neoadjuvant Chemoradiotherapy

Chien-Liang Lai
Chia-Cheng Lee
Chang-Chieh Wu
Tsai-Yu Lee
Shu-Wen Jao
Cheng-Wen Hsiao
Division of Colon and Rectal Surgery, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

Key Words
Chemoradiation therapy;
Rectum cancer;
Clinical complete response

Purpose. "Watch and Wait" policy would be the option of treatment for locally advanced rectal cancer following chemoradiotherapy with clinical complete response The short-term outcome for "Watch and Wait" has not been well established. The purpose of this work was to assess the short-term outcome of non-operative strategies.
Methods. This is an observational retrospective study of one institute. All of the patients with locally advanced rectal cancer following chemoradiotherapy with clinical complete response from January 1, 2007 to December 31, 2013 were included.
Results. The study population consisted of 18 patients. 14 patients underwent transanal wide excision of primary lesion 8-12 weeks later after chemoradiotherapy, and the remaining 4 patients were left for only observation. Two local recurrences occurred in those undergoing transanal wide excision and were successfully treated by another transanal wide excision. Average disease-free period was 69.78 months, and 5 year-overall survival rate was 100%. CEA were within normal range in 3 years follow-up.
Conclusions. "Watch and Wait" policy offers good results in terms of survival and recurrence rates, and the policy could be be considered a therapeutic option in patients with locally advanced rectal cancer follwing chemoradiation therapy with complete clinical response.
[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2015;26:109-116*]

Up to 70% of patients with non-metastatic rectal cancer present with locoregionally advanced disease.[1] Locally advanced rectal cancer (LARC) is generally defined as T3~T4 or node-positive. Neoadjuvant chemoradiotherapy (CRT) followed by a total mesorectum excision (TME) remains the globally accepted method for the management of rectal LARC.[2]

With TME, the incidence of morbidity ranges from 6% to 35%, which includes anastomotic leaks, blood loss, and sexual dysfunction resulting from the procedure. Even the mortality rate would reach up to 2%.[3] The length of hospital admissions range from 8~15 days.[4-6] There are also compelling data regarding the effect of resections on patients' quality of life. Deterioration in bowel function is common following anterior resection, and patients with rather-low lying can-

Received: March 3, 2015. Accepted: June 10, 2015.
Correspondence to: Dr. Cheng-Wen Hsiao, Division of Colon and Rectal Surgery, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, No. 325, Cheng-Kung Rd., Sec. 2, Neihu, Taipei 114, Taiwan. Tel: 886-2-8792-7191; Fax: 886-2-8792-7372; E-mail: dr.hsiao@msa.hinet.net

cers may require a permanent stoma, which would be associated with psychological morbidity.[7]

Neoadjuvant CRT has become the standard treatment for patients with LARC, allowing a reduction in local recurrence and an increasing incidence in preserving of sphincter.[8,9] Neoadjuvant CRT followed by surgery 6~8 weeks later may resume a clinical complete response (cCR) up to 15~30% of cases.[10] Also, it is associated with a lower local recurrence rate. New trends have suggested the possibility of neglecting planned surgical resections after neoadjuvant treatment in cases of extensive tumor response. In addition, more studies have addressed the use of non-operative "Watch and Wait" policy or limited resection in patients with a cCR.[8,9]

Clinical assessment of tumor response is of major concern for individualized patient management. Patients would be viewed as clinical complete responders if no visible or palpable irregularity nodule are found clinically. Habr-Gama et al. have detailed clinical and endoscopic findings of patients with a cCR; and these findings include whitening of the mucosa in the rectum, any telangiectasia, and a subtle loss of pliability of the rectal wall harboring the scar. cCR has also been described as the absence of positive signs of residual disease. Incomplete clinical response is considered in the presence of a deep ulceration, with or without a necrotic ulceration; accordingly, a palpable nodule even with mucosal complete integrity and observing of any significant stenosis.[11] Clinical appraisal for rectal cancer includes a digital rectal assessment, colonoscopy, transrectal ultrasonography (TRUS), pelvic computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET).[12,13] Current imaging techniques have been reported to be far less accurate while restaging the rectal cancer after CRT. CRT course may extensively modify cancer tissue and the surrounding structures, including the overgrowth fibrosis, wall thickness, muscle disarrangement, tumor necrosis, calcification, and inflammatory infiltration.[14] In hence, the identification of a true cCR prior surgical resection is still a challenging issue.[10]

In cases of patients with cCR treated by "Watch and Wait" policy, it is important to evaluate such a group by endoscopy as well as other image modalities (including CT scans, MRI, and TRUS).

To our knowledge, literature in validation in cCR of patients undergoing CRT in LARC is rare. Herein, we resume a retrospective study to verify "Watch and Watch" policy at our institute.

Materials and Methods

Patient selection

The study group consisted of a consecutive series of patients who underwent surgery at Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, Republic of China from 2007 to 2013 for primary rectal cancer (up to 10 cm from the anal verge). All of the patients had biopsy-verified rectal adenocarcinoma. This study was approved by Institutional Review Board of the Tri-Service General Hospital. Informed consent was obtained from all the patients.

Pre-treatment oncological staging comprised abdominal imaging (CT or MRI), and tumor marker (CEA and CA19-9 level). As a general rule, the highest stage for each parameter evaluated (T, N, circumferential margin, involvement of adjacent organ, M) was considered to be the definitive pre-treatment stage.[13,17]

Only patients of LARC undergoing complete CRT with cCR at our institute were included in the study. Patients who could not complete the CRT course, or undergo radical surgery were excluded. Those with clinical stage T0-T2, N0, and M1 status were excluded. (Fig. 1).

Treatment

Patients selected for neoadjuvant CRT were required to meet all of the following criteria: (a) a biopsy-proven rectal adenocarcinoma; (b) a tumor location up to 0~10 cm from the anal verge; (c) a primary stage of T3-4 and/or node-positive, and (d) an Eastern Cooperative Oncology Group performance status of 0-2.[2]

Five-fluorouracil (5-FU), as a single drug or in combination with other drugs (leucovorin, carboplatin or oxaliplatin), was administered by bolus or conti-

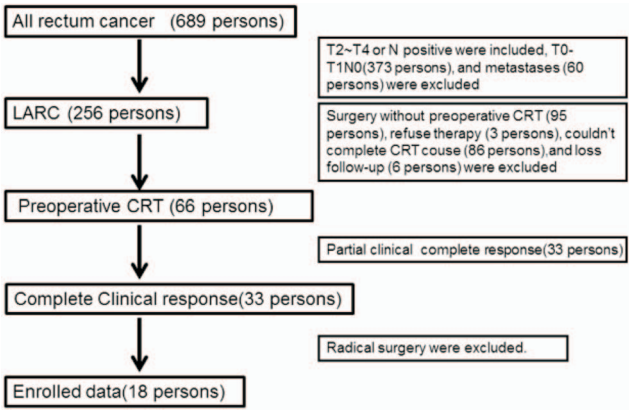

Fig. 1. Flowchart of patient selection.

nuous venous infusion (CVI). During this study, one standard regimen was used: initially, 5-FU was administered by a bolus (5-FU 350 mg/m2/day) with a low-dose leucovorin bolus (LV 10 mg/m2/day) for 5 days on days 1~5 and 29~33 in combination with RT (45 Gy in 25 fractions or 54 Gy in 30 fractions).[15]

Assessment of response and management

Patients were assessed for tumor response after 8-12 weeks from the completion of radiation therapy by the same clinical and radiologic tools used in baseline assessment of tumor extent. All patients those considered to be clinical complete responders according to rigorous criteria of clinical, endoscopic, and radiologic findings were treated without immediate radical surgery.[11] The criteria for considering cCR were the absence of residual ulceration, mass, or mucosal irregularity at clinical/endoscopic assessment. Whitening of the mucosa and the presence of neovasculature (teleangiectasia) were accepted as cCR. In addition, radiologic imaging (CT, TRUS, or MRI) without evidence of extrarectal residual disease was necessary for patients to be considered to have cCR. "Watch and Wait" policy were applied to those patients with cCR, either resuming observation or transanal wide excision.

The presence of clinical or endoscopic features of incomplete response to CRT and the radiologic evidence of residual disease within the mesorectum was diagnostic of incomplete clinical response, therefore, radical surgery was recommended. The patients with incomplete clinical response were excluded.

Follow-up

Patients with cCR were not treated by adjuvant systemic therapy regardless of their baseline staging features. Follow-up included out-patient visit every 3 months to a single experienced colorectal surgeon with clinical examination in addition to rigid proctoscopy or colonoscopy. CEA was obtained at the time of re-staging (after finishing CRT 8-12 weeks) and every 3-month interval. The third year follow-up, patients were examined every 6 months. The CEA of cutoff value is $\leqq$ 5 ng/dl at our institute. It has been demonstrated to have significant prognostic value in some studies.[16]

A radiologic imaging modality (including CT scans, and MRI) was used to exclude mesorectal disease and systemic status after 6 months and yearly thereafter. CT scans were routinely applied in all patients; however, two patients with recurrent disease underwent MRI before treatment.

Patients were completely informed that disease recurrence may develop at any moment during follow-up period. If positive nodes were identified, radical surgery would be advised. Local recurrence was defined as the presence of adenocarcinoma within the rectal wall, nodal negative, and no distal metastases by imaging scanning. Patients with local recurrence were referred for transanal wide excision.

Statistical analysis

For each patient, CEA level was collected since diagnosis, after CRT, and every 3 months follow-up. Mean CEA level was presented in Table 1. 5-year overall survival and disease-free survival rates were calculated by using the Kaplan-Meier method. (Fig. 2) The statistical analyses were performed using SPSS (ver. 15.0, SPSS Inc., Chicago, IL, USA).

Results

A total of 18 patients with locally advanced rectal cancer underwent CRT with a cCR during the study period. The demographic and clinical characteristics

Table 1. Demographic and clinical characteristics of the study group

Characteristics	N (%)/Median (±SD)
Sex	18
Men	15 (83.33%)
Women	3 (16.67%)
Age (years old)	63.78 (±14.05)
cTNM	
II	11 (61.11%)
IIIA	4 (22.22%)
IIIB	2 (11.11%)
IIIC	1 (5.56%)
Mean follow-up (months)	38.78 (±17.92)
Recurrence	2 (11.11%)
ypT1	1 (5.56%)
ypT2	1 (5.56%)
CEA level (ng/dl)	
pre-CRT CEA	1.94 (±1.08)
post-CRT CEA	2.31 (±1.34)
CEA 0.5y	1.97 (±1.57)
CEA 1y	1.98 (±1.18)
CEA 1.5y	2.08 (±0.93)
CEA 2y	2.17 (±0.81)
CEA 2.5y	2.03 (±0.44)
CEA 3y	2.06 (±0.35)

Values are expressed as N (%) of patients, unless otherwise specified.
cTNM = clinical tumor stage; yp = pathological tumor staging after neoadjuvant therapy; CRT = chemoradiation therapy; pre-CRT CEA = CEA level at pre-CRT status; post-CRT CEA = CEA level at complete CRT within 8 weeks; CEA 0.5y = CEA level after complete CRT 6 months; CEA 1y = CEA level after complete CRT 1year; CEA 1.5y = CEA level after complete CRT 1.5 years; CEA 2y = CEA level after complete CRT 2 years; CEA 2.5y = CEA level after complete CRT 2.5 years; CEA 3y = CEA level after complete CRT 3 years; SD, standard deviation.

of the study group are reported in Table 1. Clinical tumor staging was Stage II in 11 patients (61.1%), IIIA in 4 (22.22%), IIIB in 2 (11.11%), and IIIC in 1 (5.56%). Transanal wide excision was performed in 14 patients (77.78%) immediately after CRT course finished, and 4 patients (22.22%) were keep observation. After a median follow-up of 38.78 months (range, 12-84), local recurrence occurred in 2 patients (11.11%); no distant metastasis was observed in our study group. Recurrence was restricted to patients with ypT1 (1 patient, 5.56%), and ypT2 (1 patient, 5.56%). For each patient, CEA level was collected since confirmed diagnosis, after CRT, and every 3 months follow-up. (Table 1)

Disease-free survival time at a median follow-up was 69.78 months (Fig. 2A). In patients with late local recurrence (2 patients, 11.11%) underwent transanal wide excision. Overall survival rate showed 100% (Fig. 2B), and no patient of LARC with a cCR after CRT were dead in our study group.

Discussion

The treatment of patients with cCR after neoadjuvant CRT remains controversial. Some clinical trials have demonstrated that patients with cCR following a CRT have both a better oncological outcome and a lower rate of mesorectal lymph node metastases;[17] "Watch and Wait" policy and organ-sparing strategies

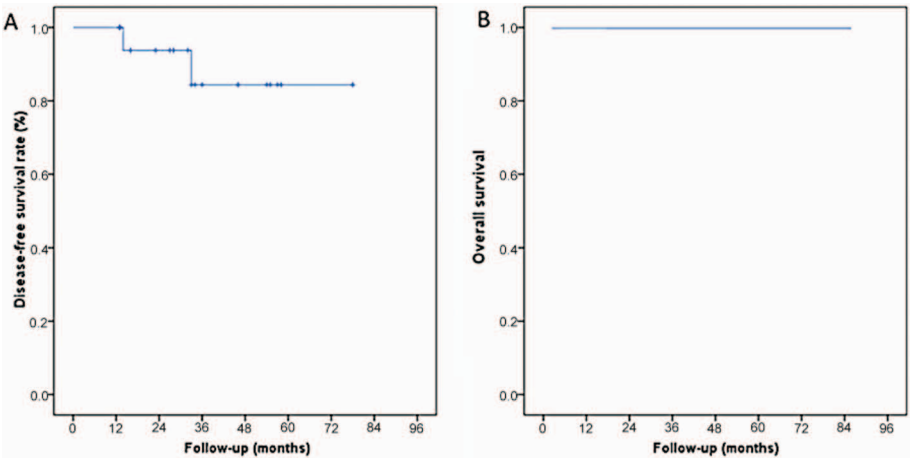

Fig. 2. Kaplan-Meier estimates for oncologic outcomes. Estimated disease-free months of non-OP were 69.78. 2B. 5-year overall survival rate was 100%.

have been advocated in such a group.[18-20] The use of alternative treatment strategies without TME is desirable to avoid the significant postoperative morbidity, unnecessary enterostoma, and outcome. Surveillance without any immediate radical surgery ("Watch and Wait" policy) may avoid postoperative complications and minimize the risk of adverse functional outcome in patients with cCR.[18-20] However, "Watch and Wait" policy after neoadjuvant CRT requires that cCR to be accurately identified by clinical and radiologic features. It would avoid the need of surgical resection exclusively for confirming pathological complete responder.

Our study group showed overall initial cCR rate was 34.85% (23/66), and disclosed the rates of 19%-30% in some studies.[10,21] These higher rates of cCR may reflect the effects in assessment of response and rapid advances in imaging technology, which both evolved throughout the study period. To avoid unnecessary surgery for LARC with a cCR after CRT, clinical assessment of post-CRT staging should be optimized. Patients were required to meet all of the following criteria as cCR: the absence of residual ulceration, mass, or mucosal irregularity at digital examination and colonoscopy assessment; whitening of the mucosa and the presence of neovasculature were accepted features of cCR; radiologic imaging (CT, TRUS, or MRI) that showed no evidence of extrarectal residual disease was required for patients to be considered to have a cCR. It may be very difficult to distinguish between residual tumor and actinic ulcers or intramural fibrosis after CRT. In our study, three experienced attending colorectal surgeons assessed clinical response to pre-treatment therapy in each patient. For this reason, this subset of patients were strictly catching the criteria described above. Nevertheless, those upon recognition of incomplete tumor regression, immediate radical surgery with TME were performed.

Follow-up included out-patient visit every 3 months to three experienced colorectal surgeons, with clinical and digital rectal examination in addition to rigid proctoscopy or colonoscopy. A radiologic imaging modality (including CT scans, MRI, and TRUS) was used to exclude mesorectal disease and systemic status after 6 months and yearly thereafter. CEA was obtained every 3 months. After 2 year of follow-up, patients were examined every 6 months.

Although several molecular tumor markers have been described over the past years, only CEA remains clinically significant for staging colorectal cancer.[22] The role of CEA in determining prognosis for colorectal cancer has been well documented not only in patients with locally advanced disease but also in those with metastatic disease.[16] One study suggested that patients with low CEA level after CRT are more likely to achieve a cCR and have better outcome.[16] Previous studies showed that neoadjuvant CRT may provide significant local tumor control, as reflected by the significant downstaging and cancer cell necrosis affected by increasing doses of radiation (and chemotherapy possibly) delivered. Therefore, post-CRT CEA status could reflect the effectiveness of neoadjuvant CRT.[16] In our data, all patients presented low CEA level < 5 ng/dl in post-CRT status (including post-CRT, 0.5 year, 1 year, 1.5 year, 2 year, 2.5 year, and 3 year follow-up time). (Table 1)

In the present study, 14 patients (77.77%) had a cCR following CRT and were treated by transanal wide excision immediately. 4 patients (22.22%) had a cCR following CRT were maintained observation alone. None of the patients developed pelvic or distal recurrence. Even though 2 patients developed a late (14 and 36 months) local recurrence, successfully treated by transanal wide excision. Interestingly, two recurrences occurred in the trananal wide excision group; however, no raised CEA level was found at the time of recurrence (CEA: 1.2 and 1.91 ng/dl, respectively). In this study, the disease-free survival in "Watch and Wait" group was a mean of 69.78 months of follow-up and 5-year overall survival rate was 100%. However, considering that no patients with a cCR were expired, it may be challenged that limited number of patients would be insufficient to allow for concluding about the appropriateness of such a treatment strategy. Based on this study, we may find that patients with cCR have a better oncologic outcome either local recurrence or distal metastasis.

There was some limitation in our study. Firstly, such a approach is primarily retrospective in single-institution. Secondly, tumor recurrences should be

considered in patients of LARC with cCR but no other radical surgical intervention. Habr-Gama et al. demonstrated that local recurrence may develop in 31% of patients with an initial cCR and that more than half of these recurrences develop within 12 months of follow-up. Salvage therapy is possible in 90% of recurrences, resulting in 94% local disease control and 78% organ preservation.[9] Thirdly, during the 7 years of the study, the facility to stage rectal cancers has improved radically, while the ability to deliver radiation therapy has also evolved dramatically. Therefore, different protocols of CRT and preoperative staging have been used over time. Moreover, low post-CRT CEA status may be associated with increasing rates of clinical complete response. However, all of 18 patients (100 percent) with a cCR in this group had a low pre-CRT CEA level, but we couldn't presume that pre-CRT CEA levels were to be a significant predictor of cCR.

Conclusion

This study may suggest the validity of "Watch and Wait" policy in LARC with cCR after CRT. Meticulous follow-up may play an important role in case of cCR to CRT. In addition, a low post-CRT CEA level is strongly related to cCR in this study. If local recurrence is present after CRT, transanal wide excision may be served as salvage treatment. From our limited experience, the patients who receive a "Watch and Wait" policy in the cCR group may benefit from avoiding TME, and also resumed adequate oncologic outcome in disease-free survival and overall survival.

Acknowledgements

We are grateful to the Cancer Registry Group of Tri-Service General Hospital from offering its data pool for the analysis.

Conflict of Interest

The authors state that there are no financial or personal relationships with other people or organizations that could inappropriately influence this work.

References

1. Gunderson LL, Jessup JM, Sargent DJ, Greene FL, Stewart A. Revised tumor and node categorization for rectal cancer based on surveillance, epidemiology, and end results and rectal pooled analysis outcomes. *J Clin Oncol* 2010;28:256-63.
2. Pomerri F, Maretto I, Pucciarelli S, Rugge M, Burzi S, Zandonà M, et al. Prediction of rectal lymph node metastasis by pelvic computed tomography measurement. *Eur J Surg Oncol* 2009;35:168-73.
3. Solanki AA, Chang DT, Liauw SL. Future directions in combined modality therapy for rectal cancer: reevaluating the role of total mesorectal excision after chemoradiotherapy. *Onco Targets Ther* 2013;6:1097-110.
4. Hartley JE, Mehigan BJ, Qureshi AE, Duthie GS, Lee PW, Monson JR. Total mesorectal excision: assessment of the laparoscopic approach. *Dis Colon Rectum* 2001;44:315-21.
5. Lujan J, Valero G, Hernandez Q, Sanchez A, Frutos MD, Parrilla P. Randomized clinical trial comparing laparoscopic and open surgery in patients with rectal cancer. *Br J Surg* 2009; 96:982-9.
6. Asoglu O, Kunduz E, Rahmi Serin K, Işcan Y, Karanlik H, Bakir B, et al. Standardized laparoscopic sphincter-preserving total mesorectal excision for rectal cancer: long-term oncologic outcome in 217 unselected consecutive patients. *Surg Laparosc Endosc Percutan Tech* 2014;24:145-52.
7. Kasparek MS, Hassan I, Cima RR, Larson DR, Gullerud RE, Wolff BG. Long-term quality of life and sexual and urinary function after abdomi- noperineal resection for distal rectal cancer. *Dis Colon Rectum* 2012;55:147-54.
8. De Nardi P, Carvello M. How reliable is current imaging in restaging rectal cancer after neoadjuvant therapy? *World J Gastroenterol* 2013;19:5964-72.
9. Habr-Gama A, Gama-Rodrigues J, São Julião GP, Proscurshim I, Sabbagh C, Lynn PB,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* 2014;88:822-8.
10. Dedemadi G, Wexner SD. Complete response after neoadjuvant therapy in rectal cancer: to operate or not to operate? *Dig Dis* 2012;30 Suppl 2:109-17.
11. Habr-Gama A, Perez RO, Nadalin W, Sabbaga J, Ribeiro U Jr, Silva e Sousa AH Jr, et al. Operative versus non-operative treatment for stage 0 distal rectal cancer following chemo- radiation therapy: long-term results. *Ann Surg* 2004;240:711-7. Discussion 711e718.
12. Martellucci J, Scheiterle M, Lorenzi B, Roviello F, Cetta F,

Pinto E, et al. Accuracy of transrectal ultrasound after preoperative radiochemotherapy compared to computed tomography and magnetic resonance in locally advanced rectal cancer. *Int J Colorectal Dis* 2012;27:967-73.

13. Mak D, Joon DL, Chao M, Wada M, Joon ML, See A, et al. The use of PET in assessing tumor response after neoadjuvant chemoradiation for rectal cancer. *Radiother Oncol* 2010;97: 205-11.
14. Pomerri F, Pucciarelli S, Maretto I, Zandonà M, Del Bianco P, Amadio L, et al. Prospective assessment of imaging after preoperative chemoradiotherapy for rectal cancer. *Surgery* 2011; 149:56-64.
15. Pucciarelli S, Friso ML, Toppan P, Fornasiero A, Carnio S, Marchiori E, et al. Preoperative combined radiotherapy and chemotherapy for middle and lower rectal cancer: preliminary results. *Ann Surg Oncol* 2000;7:38-44.
16. Perez RO, São Julião GP, Habr-Gama A, Kiss D, Proscurshim I, Campos FG, et al. The role of carcinoembriogenic antigen in predicting response and survival to neoadjuvant chemotherapy for distal rectal cancer. *Dis Colon Rectum* 2009;52: 1137-43.
17. Pucciarelli S, Capirci C, Emanuele U, Toppan P, Friso ML, Pennelli GM, et al. Relationship between pathologic T-stage and nodal metastasis after preoperative chemoradiotherapy for locally advanced rectal cancer. *Ann Surg Oncol* 2005; 12:111-6.
18. Smith JD, Ruby JA, Goodman KA, Saltz LB, Guillem JG, Weiser MR, et al. Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy. *Ann Surg* 2012;256:965-72.
19. Park JS, Jang YJ, Choi GS, Park SY, Kim HJ, Kang H, et al. Accuracy of preoperative MRI in predicting pathology stage in rectal cancers: node-for-node matched histopathology validation of MRI features. *Dis Colon Rectum* 2014;57:32-8.
20. Maas M, Beets-Tan RG, Lambregts DM, Lammering G, Nelemans PJ, Engelen SM, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. *J Clin Oncol* 2011;29:4633-40.
21. Hiotis SP, Weber SM, Cohen AM, Minsky BD, Paty PB, Guillem JG, et al. Assessing the predictive value of clinical complete response to neoadjuvant therapy for rectal cancer: an analysis of 488 patients. *J Am Coll Surg* 2002;194:131-5. Discussion 135-6.
22. Park YA, Lee KY, Kim NK, Baik SH, Sohn SK, Cho CW, et al. Prognostic effect of perioperative change of serum carcinoembryonic antigen level: a useful tool for detection of systemic recurrence in rectal cancer. *Ann Surg Oncol* 2006; 13:645-50.

原　著

“觀察及等待”應用於直腸癌化放療術後合併完全臨床反應的短期成效

賴建良　李家政　吳昌杰　李才宇　饒樹文　蕭正文

國防醫學院　三軍總醫院　外科部　大腸直腸外科

目的　“觀察及等待”治療分針對於直腸癌化放療術後合併完全臨床反應是治療上的一個選擇，但是短期成效相關數據不明，本篇目的在評估本院處理相關病患的短期成效。

方法　利用病例回顧的方式,我們回朔從 2007 年 1 月 1 日到 2013 年 12 月 31 日這六年間，直腸癌化放療術後合併完全臨床反應者被納入本篇評估。

結果　總共有 18 位病人符合篩選條件，其中 14 人在接受化放療術後 8 到 12 週有接受經肛門切除手術，其餘四位只有接受觀察追蹤。在經肛門切除手術的病人中有兩位發生局部復發，再經歷一次經肛門清除手術也獲得成功治療。平均腫瘤復發時間為 69.78 個月，五年存活率為 100%。三年內的 CEA 追蹤都在正常範圍。

結論　“觀察及等待”治療分針對於存活率及復發率好的成效，建議應用於直腸癌化放療術後合併完全臨床反應的病人。

關鍵詞　化放療、直腸癌、完全臨床反應。