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EDITORIAL

Complete radiotherapy response in rectal cancer: A review of the evidence

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Abstract

Complete response to chemoradiotherapy for rectal cancer is becoming a common clinical entity. Techniques to diagnose complete response and how to survey these patients without operative intervention are still unclear. We review the most recent evidence. Barriers to firm conclusions regarding this are heterogeneity of diagnostic definitions, differing surveillance protocols, and a lack of randomised studies.

Key words: Cancer; Rectum; Complete; Response; Chemoradiotherapy

Core tip: The management of rectal cancer has changed considerably over the last 15 years. Here we summarise the need for consensus on the definition of complete response of rectal cancer to neoadjuvant chemoradiotherapy prior to surgery, the problems associated with with heterogenous treatment programs and the need for randomised evidence.

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The concept of total mesorectal excision revolutionised the standard of care for rectal adenocarcinoma[1], vastly improving local recurrence rates from in excess of 50% to 4%-22%. Patient care was augmented further by the addition of adjuvant and neoadjuvant chemoradiotherapy (CRT)[2]. The German Rectal Cancer Trial demonstrated that patients with cT3-4 tumours with a positive nodal status benefited from a 4% local recurrence rate at 5 years when undergoing preoperative CRT compared to 13% undergoing post-operative CRT[3]. Furthermore patients with tumours in the lower third of the rectum treated with neoadjuvant CRT were 50% more likely to undergo a sphincter saving operation due to tumour involution[4]. In modern practice chemoradiotherapy followed by

surgery for rectal cancer has become the gold standard of treatment.

The risks of urinary and sexual dysfunction, faecal urgency and incontinence have, however, undoubtedly led to the development of new therapeutic approaches[5]. Local excision for T1-2 tumours has been in practice for around 15 years in anatomically accessible cancers; the conservative management of polyp cancers diagnosed retrospectively following endoscopic excision remains a key topic for research[6,7].

Of great interest is the management of patients in whom there is a complete local clinical response (cCR) to preoperative CRT. It has been shown that in post-operative specimens complete pathological response (cPR) to preoperative CRT in invasive rectal adenocarcinoma after TME is between 8% to 27% and is possible even in patients with T4 cancers[8-10]. Historically almost all cases of cCR would have then gone through completion TME. However, emerging evidence suggests that aggressive surveillance rather than progression to surgery may achieve an equal oncological and preferable quality of life outcome.

Some of the best "watchful-waiting" outcomes have been displayed by Habr-Gama. This Brazilian centre has demonstrated in several studies of up to 360 patients achieving a cCR that surgery may be delayed and substituted for an intensive clinical follow up regimen. In these studies patients initially presenting with cT3 cN0 disease had an overall 97% 5-year survival and a disease free survival of 84%, comparable to contemporaneous reviews of cPR patients treated with invasive surgery[10-12]. Within these series, 5% of patients developed a local recurrence within 2 years of initial treatment underwent salvage surgery. This is comparable to a recent Philadelphia series, which achieved an 89% disease free survival over 5 years[13]. It is noteworthy that in this study patients achieving clinical complete response had up to stage Ⅳ disease (T3N1M1), the median stage being T3N0. Of the two out of 18 patients in this group developing recurrent disease, all were resected with disease free survival within the 58-mo study period. In addition, similar non-operative studies by Maas based in the Netherlands and Smith in New York demonstrated a disease free survival of 89% and 88% and overall survival of 100% and 97% respectively[9,14].

Limitation to our confidence in the above studies arises through a limited length of follow up. Furthermore the patient selection employed by these studies is not transparent, and therefore unlikely to be population based. Although Habr-Gama has published study lengths of five years, studies beyond this time frame have suffered from patient numbers being too small to make firm conclusions[15,16].

Further considerations when interpreting this data are the heterogeneity of the studies in terms of defining and identifying cCR patients and the algorithms of surveillance.

There is no unified consensus on when and how to initially investigate patients for cCR. Of the major series, initial clinical investigation for residual tumour has begun as early as 4-6 wk, though from other authors a time frame of up to 24 wk has been accepted prior to commencing active surveillance[9,13,17,18]. Studies from Habr-Gama inspected for clinical response at eight weeks, whilst it is not clear in the Philadelphia series at which point this assessment was carried out. In addition there is a wide spectrum of cCR definition. Habr-Gama considered absence of residual ulcer on proctoscopy or adenocarcinoma-negative biopsy to be a cCR, whilst the Philadelphia series also incorporated endorectal ultrasound. An interesting paper from Wynn *et al*[19] found in excess of seventy descriptions of complete response within the United Kingdom alone calling for an international, if not only a national classification of response. No one clear definition within current literature appears dominant over the other.

Should we give a wide freedom to the definition of cCR, the method of diagnosing complete clinical response within the published literature is also heterogeneous. The problem of differentiating residual tumour from juvenile scarring or inflammatory change continues to provide a clinical challenge. The investigations we rely upon for accurate initial staging at first diagnosis have not been found to be reliable following CRT.

Inaccuracy of digital rectal examination following CRT within in the office, clinic or at the time of operation has been well demonstrated, with a negative predictive value of between 21% to 24%[20-22]. Coupled with clinical examination, endoscopic assessment with biopsy has been shown to possess a false negative rate of 69%, though its merit perhaps being found to be a 0% false positive rate[23].

Endorectal ultrasound (EUS) has gained popularity over the last ten years as it has been demonstrated to accurately stage rectal tumours prior to any therapy[24]. However this accuracy has not been reproduced post radiotherapy. Maretto *et al*[23] demonstrated a 77% sensitivity in EUS T stage assessment following CRT, though only a 33% specificity. However EUS possessed an 81% negative predictive value for assessing involvement of lymph nodes, compared with only a 65% negative predictive value for MRI in lymph node status in the same study[23]. Other studies supported these findings demonstrating 63% and 54% accuracy in assessing T stage of rectal tumours (including T0), with a 77% and 75% negative predictive value for lymph node involvement respectively[25,26]. The poor reliability of EUS as a diagnostic tool following CRT has been echoed elsewhere in the literature, and therefore has not been previously advocated as a surveillance tool[27].

The use of MRI has in recent literature been named as the gold standard in post CRT tumour assessment. A large meta-analysis including 1556 patients found that MRI possessed a 50% sensitivity but a 91%

specificity for T stage, with a sub group analysis showing a 19% sensitivity and 94% specificity for T0 tumours[28]. With the addition of DWI and dynamic contrast imaging within the last few years the overall sensitivity and specificity in the context of post CRT assessment was found to rise to 84% and 85% respectively. It was also found in this study that there was only a 77% sensitivity and 60% specificity for nodal involvement. Another smaller study identified a 65% negative predictive value for N0 status[23], and more recently a study of 150 patients found that MRI tended to over-stage nodal spread[29] reinforcing a potential weakness of using MRI alone for assessment of tumour and nodal involution. Recently the use of T2 weighted MRI was demonstrated to provide an accuracy of 92% in identifying complete responders in terms of local disease.

Lastly PET CT has been investigated as a potential imaging modality. Cho *et al*[30] identified only a 60% accuracy in correctly identifying complete tumour response, with a 71% accuracy for nodal metastases. These findings were also supported from an early study showing high false positive and low false negative rates for residual tumour detection. The strength of PET CT however was argued by Cho to be in identifying early distant metastases, with a sensitivity of 97%.

We may therefore glean from these studies that no imaging modality appears superior to others in assessing the primary tumour site, the mesorectum nor nodal tumour spread. Pucciarelli *et al*[31] in 2005 suggested that in the context of patients presenting with T2 tumours subsequently achieving cCR using several imaging modalities, the mesorectal involvement rate might still be as high as 17% at resection. It is perhaps for this reason that patients in published series entering into an active surveillance program have undergone a full complement of proctoscopy, EUS, endoscopic biopsy, MRI and CT. Certainly the larger more recent retrospective studies from Habr-Gama and Smith assessed subjects along all modalities. Interestingly a review combining 545 patients who achieved cCR following CRT found that 6% had either mesorectal tumour deposits or nodal involvement not identified before surgery, which some clinicians may argue is an unacceptably high miss rate[32].

We may therefore summarise that although the conservative management of cCR promises a preferable alternative to invasive surgery we currently lack several consensuses. Firstly the limit of acceptable CRT prior to achieving complete clinical response has not yet been established. Secondarily of paramount importance is the unified definition of cCR. Furthermore when the assessment of tumour and nodal involution is to take place, and if a conservative approach is to be adopted, by what modalities, when and for how long should surveillance persist? It would be preferable that these consensuses are defined prior to any randomised studies.

Finally it is of note that patients undergoing cCR or cPR have an improved disease free and overall survival than those who have a partial response[33]. Although this may not appear to be surprising at first glance this may demonstrate a cohort of patients who may be identifiable prior to CRT based upon tumour genetics or other factors, and therefore be entered into a conservative programme with curative intent without surgery. Currently there are no published data regarding tumour genetics in these cases, but early regression analysis has shown that these patients, in addition to being male and older than their operative counterparts, tend to have tumours in the lower third of the rectum. Of course several sources of bias come into play in this setting such as patient attitudes towards permanent or temporary stoma formation and fitness for surgery but nevertheless this may pose an enticing avenue of future research.

REFERENCES

1 **MacFarlane JK**, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. *Lancet* 1993; **341**: 457-460 [PMID: 8094488 DOI: 10.1016/0140-6736(93)90207-W]

2 **Kapiteijn E**, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, Rutten HJ, Pahlman L, Glimelius B, van Krieken JH, Leer JW, van de Velde CJ. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001; **345**: 638-646 [PMID: 11547717 DOI: 10.1056/NEJMoa010580]

3 **Sauer R**, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, Martus P, Tschmelitsch J, Hager E, Hess CF, Karstens JH, Liersch T, Schmidberger H, Raab R. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004; **351**: 1731-1740 [PMID: 15496622 DOI: 10.1056/NEJMoa040694]

4 **Callender GG**, Das P, Rodriguez-Bigas MA, Skibber JM, Crane CH, Krishnan S, Delclos ME, Feig BW. Local excision after preoperative chemoradiation results in an equivalent outcome to total mesorectal excision in selected patients with T3 rectal cancer. *Ann Surg Oncol* 2010; **17**: 441-447 [PMID: 19847569 DOI: 10.1245/s10434-009-0735-7]

5 **Russell MM**, Ganz PA, Lopa S, Yothers G, Ko CY, Arora A, Atkins JN, Bahary N, Soori GS, Robertson JM, Eakle J, Marchello BT, Wozniak TF, Beart RW, Wolmark N. Comparative effectiveness of sphincter-sparing surgery versus abdominoperineal resection in rectal cancer: patient-reported outcomes in National Surgical Adjuvant Breast and Bowel Project randomized trial R-04. *Ann Surg* 2015; **261**: 144-148 [PMID: 24670844 DOI: 10.1097/SLA.0000000000000594]

6 **Freeman HJ**. Long-term follow-up of patients with malignant pedunculated colon polyps after colonoscopic polypectomy. *Can J Gastroenterol* 2013; **27**: 20-24 [PMID: 23378979]

7 **Amann M**, Modabber A, Burghardt J, Stratz C, Falch C, Buess GF, Kirschniak A. Transanal endoscopic microsurgery in treatment of rectal adenomas and T1 low-risk carcinomas. *World J Surg Oncol* 2012; **10**: 255 [PMID: 23181563 DOI: 10.1186/1477-7819-10-255]

8 **Gérard JP**, Chamorey E, Gourgou-Bourgade S, Benezery K, de Laroche G, Mahé MA, Boige V, Juzyna B. Clinical complete response (cCR) after neoadjuvant chemoradiotherapy and conservative treatment in rectal cancer. Findings from the ACCORD 12/PRODIGE 2 randomized trial. *Radiother Oncol* 2015; **115**: 246-252 [PMID: 25921382 DOI: 10.1016/j.radonc.2015.04.003]

9 **Maas M**, Beets-Tan RG, Lambregts DM, Lammering G, Nelemans PJ, Engelen SM, van Dam RM, Jansen RL, Sosef M, Leijtens JW, Hulsewé KW, Buijsen J, Beets GL. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. *J Clin Oncol* 2011; **29**: 4633-4640 [PMID: 22067400 DOI: 10.1200/

JCO.2011.37.7176]
10 **Habr-Gama A**, Perez RO, Nadalin W, Sabbaga J, Ribeiro U, Silva e Sousa AH, Campos FG, Kiss DR, Gama-Rodrigues J. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. *Ann Surg* 2004; **240**: 711-717; discussion 717-718 [PMID: 15383798 DOI: 10.1097/01.sal.0000141194.27992.32]
11 **Habr-Gama A**, Perez RO, Proscurshim I, Campos FG, Nadalin W, Kiss D, Gama-Rodrigues J. Patterns of failure and survival for nonoperative treatment of stage c0 distal rectal cancer following neoadjuvant chemoradiation therapy. *J Gastrointest Surg* 2006; **10**: 1319-1328; discussion 1328-1329 [PMID: 17175450 DOI: 10.1016/j.gassur.2006.09.005]
12 **Smith FM**, Rao C, Oliva Perez R, Bujko K, Athanasiou T, Habr-Gama A, Faiz O. Avoiding radical surgery improves early survival in elderly patients with rectal cancer, demonstrating complete clinical response after neoadjuvant therapy: results of a decision-analytic model. *Dis Colon Rectum* 2015; **58**: 159-171 [PMID: 25585073 DOI: 10.1097/DCR.0000000000000281]
13 **Smith RK**, Fry RD, Mahmoud NN, Paulson EC. Surveillance after neoadjuvant therapy in advanced rectal cancer with complete clinical response can have comparable outcomes to total mesorectal excision. *Int J Colorectal Dis* 2015; **30**: 769-774 [PMID: 25787162 DOI: 10.1007/s00384-015-2165-2]
14 **Smith JD**, Ruby JA, Goodman KA, Saltz LB, Guillem JG, Weiser MR, Temple LK, Nash GM, Paty PB. Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy. *Ann Surg* 2012; **256**: 965-972 [PMID: 23154394 DOI: 10.1097/SLA.0b013e3182759f1c]
15 **Yeo SG**, Kim DY, Oh JH. Long-term survival without surgery following a complete response to pre-operative chemoradiotherapy for rectal cancer: A case series. *Oncol Lett* 2013; **6**: 1573-1576 [PMID: 24260048 DOI: 10.3892/ol.2013.1596]
16 **Kong M**, Hong SE, Choi WS, Kim SY, Choi J. Preoperative concurrent chemoradiotherapy for locally advanced rectal cancer: treatment outcomes and analysis of prognostic factors. *Cancer Res Treat* 2012; **44**: 104-112 [PMID: 22802748 DOI: 10.4143/crt.2012.44.2.104]
17 **Habr-Gama A**, Perez RO, Sabbaga J, Nadalin W, São Julião GP, Gama-Rodrigues J. Increasing the rates of complete response to neoadjuvant chemoradiotherapy for distal rectal cancer: results of a prospective study using additional chemotherapy during the resting period. *Dis Colon Rectum* 2009; **52**: 1927-1934 [PMID: 19934911 DOI: 10.1007/DCR.0b013e3181ba14ed]
18 **Dalton RS**, Velineni R, Osborne ME, Thomas R, Harries S, Gee AS, Daniels IR. A single-centre experience of chemoradiotherapy for rectal cancer: is there potential for nonoperative management? *Colorectal Dis* 2012; **14**: 567-571 [PMID: 21831177 DOI: 10.1111/j.1463-1318.2011.02752.x]
19 **Wynn GR**, Bhasin N, Macklin CP, George ML. Complete clinical response to neoadjuvant chemoradiotherapy in patients with rectal cancer: opinions of British and Irish specialists. *Colorectal Dis* 2010; **12**: 327-333 [PMID: 19555388 DOI: 10.1111/j.1463-1318.2009.01962.x]
20 **Hiotis SP**, Weber SM, Cohen AM, Minsky BD, Paty PB, Guillem JG, Wagman R, Saltz LB, Wong WD. 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**: 131-135; discussion 135-135 [PMID: 11848629 DOI: 10.1016/S1072-7515(01)01159-0]
21 **Guillem JG**, Chessin DB, Shia J, Moore HG, Mazumdar M, Bernard B, Paty PB, Saltz L, Minsky BD, Weiser MR, Temple LK, Cohen AM, Wong WD. Clinical examination following preoperative chemoradiation for rectal cancer is not a reliable surrogate end point. *J Clin Oncol* 2005; **23**: 3475-3479 [PMID: 15908656 DOI: 10.1200/JCO.2005.06.114]
22 **Kahn H**, Alexander A, Rakinic J, Nagle D, Fry R. Preoperative staging of irradiated rectal cancers using digital rectal examination, computed tomography, endorectal ultrasound, and magnetic resonance imaging does not accurately predict T0,N0 pathology. *Dis Colon Rectum* 1997; **40**: 140-144 [PMID: 9075746 DOI: 10.1007/BF02054977]
23 **Maretto I**, Pomerri F, Pucciarelli S, Mescoli C, Belluco E, Burzi S, Rugge M, Muzzio PC, Nitti D. The potential of restaging in the prediction of pathologic response after preoperative chemoradiotherapy for rectal cancer. *Ann Surg Oncol* 2007; **14**: 455-461 [PMID: 17139456 DOI: 10.1245/s10434-006-9269-4]
24 **Hünerbein M**. Endorectal ultrasound in rectal cancer. *Colorectal Dis* 2003; **5**: 402-405 [PMID: 12925070 DOI: 10.1046/j.1463-1318.2003.00516.x]
25 **Vanagunas A**, Lin DE, Stryker SJ. Accuracy of endoscopic ultrasound for restaging rectal cancer following neoadjuvant chemoradiation therapy. *Am J Gastroenterol* 2004; **99**: 109-112 [PMID: 14687151 DOI: 10.1046/j.1572-0241.2003.04019.x]
26 **Pastor C**, Subtil JC, Sola J, Baixauli J, Beorlegui C, Arbea L, Aristu J, Hernandez-Lizoain JL. Accuracy of endoscopic ultrasound to assess tumor response after neoadjuvant treatment in rectal cancer: can we trust the findings? *Dis Colon Rectum* 2011; **54**: 1141-1146 [PMID: 21825895 DOI: 10.1097/DCR.0b013e31821c4a60]
27 **Williamson PR**, Hellinger MD, Larach SW, Ferrara A. Endorectal ultrasound of T3 and T4 rectal cancers after preoperative chemoradiation. *Dis Colon Rectum* 1996; **39**: 45-49 [PMID: 8601356 DOI: 10.1007/BF02048268]
28 **van der Paardt MP**, Zagers MB, Beets-Tan RG, Stoker J, Bipat S. Patients who undergo preoperative chemoradiotherapy for locally advanced rectal cancer restaged by using diagnostic MR imaging: a systematic review and meta-analysis. *Radiology* 2013; **269**: 101-112 [PMID: 23801777 DOI: 10.1148/radiol.13122833]
29 **Lee JH**, Jang HS, Kim JG, Lee MA, Kim DY, Kim TH, Oh JH, Park SC, Kim SY, Baek JY, Park HC, Kim HC, Nam TK, Chie EK, Jung JH, Oh ST. Prediction of pathologic staging with magnetic resonance imaging after preoperative chemoradiotherapy in rectal cancer: pooled analysis of KROG 10-01 and 11-02. *Radiother Oncol* 2014; **113**: 18-23 [PMID: 25245559 DOI: 10.1016/j.radonc.2014.08.016]
30 **Cho YB**, Chun HK, Kim MJ, Choi JY, Park CM, Kim BT, Lee SJ, Yun SH, Kim HC, Lee WY. Accuracy of MRI and 18F-FDG PET/CT for restaging after preoperative concurrent chemoradiotherapy for rectal cancer. *World J Surg* 2009; **33**: 2688-2694 [PMID: 19823904 DOI: 10.1007/s00268-009-0248-3]
31 **Pucciarelli S**, Capirci C, Emanuele U, Toppan P, Friso ML, Pennelli GM, Crepaldi G, Pasetto L, Nitti D, Lise M. Relationship between pathologic T-stage and nodal metastasis after preoperative chemoradiotherapy for locally advanced rectal cancer. *Ann Surg Oncol* 2005; **12**: 111-116 [PMID: 15827790 DOI: 10.1245/ASO.2005.03.044]
32 **Glynne-Jones R**, Hughes R. Critical appraisal of the 'wait and see' approach in rectal cancer for clinical complete responders after chemoradiation. *Br J Surg* 2012; **99**: 897-909 [PMID: 22539154 DOI: 10.1002/bjs.8732]
33 **Martin ST**, Heneghan HM, Winter DC. Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer. *Br J Surg* 2012; **99**: 918-928 [PMID: 22362002 DOI: 10.1002/bjs.8702]

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