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Current Status of the Watch-and-Wait Policy for Patients with Complete Clinical Response Following Neoadjuvant Chemoradiation in Rectal Cancer

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Abstract Preoperative chemoradiation is the standard of care for patients with locally advanced rectal cancer to reduce the risk of local recurrence. Chemoradiation can achieve a pathological complete response (pCR) in 10–20% of patients when surgery is performed at 4–12 weeks following completion, and a clinical complete response (cCR) in 15–30% if surgery is withheld. The probability of pCR and cCR is partly dependent on initial clinical T- and N-stage. Observational/retrospective studies suggest a selective watch-and-wait policy with rigorous surveillance, avoiding radical surgery, is a safe option to offer patients who achieve a cCR or near cCR. With a watch-and-wait approach, approximately one third will relapse within 12 months, but regrowth is almost invariably endoluminal, and can often be salvaged without compromising overall survival. The aim of this overview is to examine the current status of the watch-and-wait policy for patients with cCR following chemoradiation in rectal cancer.

Keywords Rectal cancer · Radiotherapy · Brachytherapy · Contact X-ray therapy · Chemoradiation · Preoperative · Dose-response · Complete clinical response · Non-operative management · Non-surgical management · Avoidance of surgery · Deferral of surgery · 'Watch-and-wait' · 'Wait and see' · Omission of surgery · Observation · Organ sparing

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Introduction

Preoperative chemoradiation (CRT) is recommended for patients with locally advanced rectal cancer (LARC) to reduce local pelvic recurrence [1–4]. In these patients, CRT represents the current standard of care [5, 6] where the combination of optimal quality surgery with total mesorectal excision (TME) and the addition of preoperative radiotherapy has reduced local recurrence and the surgical advances in particular have improved overall survival [7–10]. CRT can achieve a complete pathological response (pCR) in 10–20% of patients when surgery is performed at 4–12 weeks following completion, and a complete clinical response (cCR) in 15–30% if surgery is withheld.

However, radical surgery entails a permanent colostomy in 10–30% of patients, more so if the site of the cancer is low close to the sphincteric muscles where an abdominoperineal excision of the rectum (APER) is required. Such surgery is associated with alteration in body image leading to significant physical and psychological morbidity [11, 12]. With this expectation, many patients express a strong desire to avoid a colostomy [13]. In addition, even with higher tumours, where an anterior resection can be performed, patients often require a temporary stoma which is never reversed in 20–50% of patients [14, 15]. The probability of stoma reversal is compromised by both short course preoperative radiotherapy (SCPRT) and CRT [8, 16]. Even if sphincter preservation is achieved, bowel function is often poor because of 'low anterior resection syndrome' or LARS [17] which is worsened further by both CRT and SCPRT [18•]. CRT will also adversely affect urinary and sexual function [19].

The mortality rate after TME surgery is at least 2% even in the medically fit and higher in older adults over 75 where 15–25% of patients may die within 6 months of surgery [9, 20]. Surgical morbidity ranges from 6 to 35%, which includes

anastomotic leak, pelvic sepsis, poor healing, fistulae and blood loss, all of which can deter informed patients from accepting radical surgery.

If radical surgery is performed with a permanent stoma, only to find no viable residual tumour cells, the procedure may be perceived retrospectively as an unnecessary risk in terms of mortality, surgical morbidity and long-term quality of life. Hence, some surgeons actively promote a watch-and-wait policy if cCR is observed after CRT [21].

Population data suggests that patients are increasingly avoiding radical surgery in the USA [22, 23], perhaps leading to a shorter overall survival (OS) compared to CRT and surgery, with 3- and 5-year OS rates of 71.34 versus 88.29% and 58.21 versus 77.12%, respectively. However, the authors were unable to clarify whether patients achieved a cCR or whether they simply failed to undergo surgery [24]. Angelita Habr Gama has pointed out that simply avoiding surgery is not necessarily the same strategy—nor has the same outcomes as a watch-and-wait policy in the face of complete clinical response [25].

Although neoadjuvant CRT does not improve DFS or OS, the extent of tumour response to neoadjuvant CRT is an independent prognostic factor, and cCR is a biomarker for an excellent oncological outcome—whether the patient undergoes radical resection or is included in a watch-and-wait programme. However, up to 30% of patients do not show any clinical or histopathological response to CRT [26, 27]. Patients who do not achieve a cCR may be disadvantaged by delaying definitive surgery because the tumour is observed to be shrinking. The regrowth of viable cells could increase the risk of local and distant progression especially where a cancer is deemed initially resectable but close to the mesorectal fascia, i.e. threatening a potentially involved radial margin, and potentially an R1 resection.

Studies examining a watch-and-wait strategy are not randomised and enrolment is biased by patient self-selection, selection of small early tumours and concerns regarding comorbidity. Consequently, oncological outcomes should remain under scrutiny. Also, there are few reports of long-term mature functional outcomes and quality of life (QOL) [28, 29••]. Without prospective trials which show the denominator, it is difficult to assess how often a cCR can be achieved for each clinical stage and hence how to counsel a patient in advance. Recent small studies from Brazil suggest between 30 and 50% of early cancers could be appropriate for a watch-and-wait approach [30, 31]. After a follow-up of 12 months, 56% of patients had a sustained cCR [29••], but 44% had experienced regrowth.

The assessment of tumour response to preoperative CRT is based on pCR, the degree of primary tumour (ypT) and nodal (ypN) down-staging and the histopathological tumour regression grade (TRG), all of which correlate significantly in the individual with local recurrence and survival outcomes [27, 32]. The conventional interval of 4–8 weeks between the completion of CRT and surgery leads to a 10–20% pCR rate [33]. Despite pCR in the primary, residual disease in the mesorectal lymph nodes has been reported in up to one sixth of patients [34]. Population studies also report that if surgery is undertaken after 4 weeks, up to 16% of patients may be diagnosed with ypT0 ypN1-2 [35•]. Although residual micrometastases in lymph nodes with deposits <0.2 cm may have less prognostic impact [36], especially if surgery takes place early before the cells have had sufficient time elapsed to allow them to disappear. Hence, there is an ongoing search for relevant clinical markers to predict pCR in both primary and mesorectal nodes at the initial staging and also following CRT.

Views regarding the appropriateness of this selective watch-and-wait approach are highly polarised. Some remain unsatisfied with the evidence and continue to advocate prospective clinical trials to show equivalence in survival, local recurrence rates, or other relevant outcomes, before watch-and-wait can be adopted as an appropriate standard-of-care option [36].

The aim of this discussion is to critically review the current status of the watch-and-wait policy for patients who achieve a cCR following neoadjuvant CRT in rectal cancer. We have examined the medical literature, using the endpoints of local recurrence/local regrowth, metastatic disease, disease-free survival (DFS), OS, functional outcomes, feasibility of salvage surgery, morbidity and quality of life (QoL).

Methods

We updated previous reviews [33, 37] of non-operative management in LARC. We identified studies with the terms rectal cancer; neoadjuvant chemoradiotherapy; pathologic complete response; complete clinical response; selective non-operative management after neoadjuvant chemoradiotherapy; watch-and-wait, imaging of response and surveillance. Retrospective observational and case-control series, as well as prospective cohort and Phase I, II and III clinical trials, were included. The primary outcome measure was cCR. Secondary outcome measures included locoregional failure (LRF), the rate of successful salvage surgery, the rate of metastases, DFS and OS and anorectal function/quality of life.

Results

The largest experience of a watch-and-wait policy was derived from Brazil [30, 31, 38–51, 52•]. The original series [37] reported on 118 patients with low rectal cancer (within 7 cm of the anal verge), who underwent watch-and-wait. A total of 36/118 (30%) achieved a cCR, defined by an inability to see or feel tumour on inspection and digital rectal examination (DRE), radiological imaging and the addition of a negative

biopsy. Local failure was observed in 8/118 (all with endoluminal regrowth) and required salvage resection within 3–14 months, but experienced similar local recurrence and survival to patients found to have achieved a pCR at surgery. Subsequent papers [39, 46] with additional patients have refined the results and the methodology more robustly.

Another series from the Netherlands reported on 21 patients achieving a clinical cCR after CRT [53]. A recent update reports on a further 79 patients achieving organ preservation [29••]. This study, acknowledges that a small percentage of patients cannot be successfully salvaged. Some early retrospective reports in elderly or frail patients are poorly documented [54–56]. Further, small single-institution series have reported a more meticulous watch-and-wait approach [57–68]. A larger propensity-matched analysis [69] also supports the feasibility of a watch-and-wait approach. All studies outside Brazil suggest only a small proportion of patients receiving CRT actually achieve a sustained cCR.

Selection of the Most Appropriate Patients

Reliable biomarkers to accurately predict response or resistance prior to CRT could avoid the long-term toxicity of radiation in those who would unlikely benefit from radiotherapy, but allow others who are likely to respond with a cCR to be spared radical surgery.

MRI offers a reasonably accurate method of providing an exact clinical T-staging with a quantifiable precise evaluation of the relationship of extraluminal tumour to the mesorectal fascia (MRF), the levator muscles in the low rectum and the peritoneal reflection [70]. The initial tumour T-stage predicts post CRT outcomes. In the French GRECCAR 2 phase III trial [71], patients with cT2/T3 low rectal carcinomas (size ≤4 cm), i.e. small T2/T3, demonstrated higher pCR rates than more advanced T3/T4 tumours (40 vs 15%). If early cT2 tumours are selected for CRT with an intent of avoiding radical surgery, then ypT0 can be achieved in the primary site after local excision in almost 50% [72]. In contrast, few if any clinically staged T4 cancers [27] achieve pCR. Additionally, a recent study demonstrated that in patients requiring multivisceral resection, only 3/56 (5.4%) achieved pCR [73].

Small retrospective studies have proposed additional clinical factors and molecular biomarkers as possible predictors of tumour response or lack of response to preoperative CRT, which include tumour size location, circumferential involvement and a baseline carcinoembryonic antigen (CEA) level [74]. However, reliable pre-treatment markers of tumour resistance or sensitivity are lacking. The role of KRAS and BRAF mutations are implicated in resistance to anti-EGFR agents in metastatic disease, but studies have not shown a role in predicting response to irradiation. However, patients with BRAF, NRAS, APC or TP53 mutations rarely if ever achieve a pCR [75]. Histopathological parameters are also important as mucinous tumours respond poorly, and in particular signet ring differentiation is more resistant to 5FU-based chemoradiation [76]. Others suggest biomarkers of cellular hypoxia and expression of proteins such as COX2 and CD133 are relevant. Yet, no robust markers of the prediction of pCR have yet been identified.

Post CRT Factors to Predict pCR/cCR

There are no reliable clinical or radiological factors that can robustly predict pCR after preoperative CRT. Imaging techniques such as MRI and PET scanning have been commonly explored, but correlations between other clinical factors following CRT and achievement of a pCR are seldom examined and remain poorly defined [77]. Magnetic resonance tumour regression grade (mrTRG) appears more effective at diagnosing a pCR than the endoluminal mucosal appearances [78]. The change in CEA from initial levels predicts response to preoperative CRT in LARC [79].

What Is the Optimal Radiotherapy and Chemotherapy Schedule/Treatment to Achieve cCR

Investigators have explored a number of different strategies to intensify treatment to increase the rate of cCR without adversely affecting long-term functional outcomes. The standard for preoperative CRT is a relatively modest total dose of radiation (45–50.4 Gy) with conventional fractionation (1.8–2.0 per fraction), which has remained virtually unchanged over decades. Habr Gama currently uses a higher total dose by boosting the primary site to 54 Gy. Data on toxicity and late function has not been reported for this higher dose.

Intensity-modulated radiotherapy (IMRT), volumetric arc therapy and image-guided radiotherapy may allow us to reduce doses to organs at risk (OAR), such as small bowel, bladder and femur heads, and improve tolerance [80, 81]. IMRT may also allow future opportunities to dose-escalate the radiotherapy [82] and possibly increase the cCR rate. Yet, randomised data to support higher doses of radiotherapy is lacking [83].

Contact brachytherapy may be useful to administer very high doses in three or four large fractions to small early tumours [84]. Endoluminal brachytherapy may also be used to boost the dose to the primary tumour in more advanced cases, but randomised trials have not shown an increase in pCR with such boosts [85]. Both tumour size and clinical nodes (cN) category may modify the dose-response relationships [86] particularly in the context of pCR.

With contact brachytherapy, the volume irradiated appears mainly limited to an approximate 2 cm radius from the primary tumour and hence provides limited dose to the more distant mesorectal lymph nodes. Thus, higher doses to primary tumour may increase ypT0 rate but are less likely to impact on

the overall pathological complete response rate (ypT0N0). A theoretical model suggests at least 90 Gy to the primary tumour would be required to achieve a pCR in 50% of cases [86]. Such doses cannot be delivered safely via external beam treatments and would require the use of brachytherapy techniques either as a primary treatment or as local boosts.

A prospective study in small early cancers used a dose escalation of radiotherapy within CRT (60 Gy in 30 fractions to primary tumour, 50 Gy in 30 fractions to elective lymph node volumes and a 5 Gy endorectal brachytherapy boost) [65]. In total, 40 patients achieved a cCR with a median follow-up of 23.9 months, and local recurrence at 1 year was only 15.5%. Sphincter function was good. The majority, 11/16 (69%) patients, reported no faecal incontinence, although a few patients reported grade 3 bleeding at 2 years.

The ACOSOG Z6041 trial integrated oxaliplatin into a CRT schedule followed by local excision in patients with cT2N0 distal rectal cancers as an organ preservation strategy [71]. Using this protocol, 72/79 patients (91%) preserved their rectum. However, the results of large randomised phase III trials evaluating the addition of oxaliplatin have been generally disappointing. In the majority of these trials (**STAR-01**, **ACCORD 12/0405-Prodige 2**, **NSABP R-04**, **PETTAC-6**), the oxaliplatin CRT arm was associated with a significant increase in grade 3–4 acute gastrointestinal toxicity without any benefit in terms of local control, DFS or OS. Two trials showed an increase in the pCR rate [87, 88], but the increase was only statistically significant in the German trial [88]. Although the ACOSOG Z6041 trial failed to demonstrate any deterioration in function (FISI or FACT-C scores) at 1 year after CRT and surgery [71], it remains unclear whether any of these intensification strategies adversely affect long-term functional outcomes because late function has rarely been measured.

Hence, there is little support for schedules which deliver a total dose in excess of 54 Gy and the current authors recommend 50.4 Gy with oral capecitabine as the standard CRT. Recent trials using SCPRT without chemotherapy and waiting have shown similar rates of down-staging to CRT, and this represents a very well-tolerated option in the elderly or those with co-morbidity. The Polish group have demonstrated a pCR rate of 16% with SCPRT followed by 3 cycles of Folfox neoadjuvant chemotherapy and reassessment after 12 weeks prior to surgery [89]. If the options for dose escalation of the radiotherapy are limited, then future strategies may concentrate on increasing the use of neoadjuvant chemotherapy or integrating biological or immune-based treatments, which potentially avoid overlapping toxicity and may reduce late radiation toxicities.

Optimal Assessments to Define cCR

Complete clinical response has only partial concordance with pCR. cCR can be indicated by failure to find tumour on digital rectal examination (DRE); endoscopic luminal assessment; and locoregional imaging, but cCR is not a robust endpoint because it is open to interpretation. Endoscopic assessment can complement DRE by showing shallow ulceration or more subtle mucosal irregularity. Hence, endoscopic surveillance after CRT may be the single most accurate modality for identifying cCR [90, 91].

Biopsy after CRT can lead to poor healing, scarring and poor function. Sampling error leads to the poor accuracy of biopsy after CRT. Clearly, if the biopsy is positive, then this is definitive (although a further interval may allow further ongoing response). A negative biopsy at the primary site presents obvious limitations because the status of the mesorectal lymph nodes (LN), pelvic LN and lateral pelvic LN is not sampled. In one retrospective study [92], patients who achieved an incomplete clinical response after neoadjuvant CRT, only three patients with a negative biopsy, had a complete pathological response (giving a negative predictive value of only 21%). Even full-thickness incisional biopsies taken directly underneath the most obvious residual mucosal abnormality offers a sensitivity of only 50% [93]. In contrast, lateral tumour spread beneath an adjacent apparently normal mucosa can extend up to 9 mm [94].

Studies using CT, MRI and EUS show poor accuracy in predicting pCR in the primary tumour [95]. Larger more advanced tumours tend to demonstrate fragmented patterns of regression after CRT [96]. None of the imaging modalities are precise in their ability to distinguish post-radiation fibrosis from residual disease in the primary site—particularly if the tumour has fragmented into small microscopic foci. Hence, these imaging modalities can simultaneously both underestimate and overestimate pathological T-stage. Thus, their overall sensitivity in identifying ypT0 is poor [97]. However, CT, MRI or positron emission tomography (PET) capture quite well the changes in mesorectal and pelvic nodes, and MRI post CRT appears to have a high negative predictive value in mesorectal nodes [98]. A combination approach utilising these modalities may offer the best yield. Standard T2-weighted/diffusion-weighted MRI, DRE, proctoscopy and selective biopsy result in a specificity of >90% [99]. More recently, post-treatment MRI reassessment using mriTRG appears the most robust and effective method of differentiating between good and intermediate or poor responders to CRT. As these strategies are less technician dependent, reasonable reproducibility is likely obtained [100].

The utility of CT imaging alone is largely restricted to the detection of metastatic disease and has low sensitivity in predicting ypT0 after CRT. However, combined with other strategies (i.e. PET/CT), more information might be obtained.

PET imaging allows assessment of functional tumour activity. A decrease in the SUVmax on PET/CT of >67% between baseline and 6-week or 76% between baseline and 12-week SUVmax appear associated with complete response [49]. Nomograms using PET imaging and clinical factors have also been proposed to improve the accuracy of prediction

[101]. PET/CT [102] and contrast-enhanced or diffusion-weighted [103] MRI are generally regarded as the most accurate methods of monitoring response to neoadjuvant CRT in rectal cancer. Hence, optimal post-treatment assessment should be based on imaging and endoluminal visualisation complemented by sequential DRE—ideally by the same clinician.

Optimal Timing of Assessments and Is It Worth Waiting Longer?

A watch-and-wait strategy requires meticulous endoscopic and radiographic surveillance at regular frequent intervals over the long term. Extending the time between the completion of CRT and surgery may increase the rate of pCR and cCR. Population data and several retrospective studies suggest that there may be an advantage by extending assessment up to about 16 weeks following completion of treatment rather than the standard 6–10 weeks. However, randomised studies specifically addressing the interval have failed to show a consistent benefit from a longer interval, which may be associated with greater surgical morbidity [104•, 105•].

Should Additional Chemotherapy/'Adjuvant' Chemotherapy Be Administered

Additional systemic 'adjuvant' chemotherapy before surgery could increase the numbers who respond and enhance the depth of response both locally and distally and enable more patients to be managed non-operatively. In series where radical surgery is performed after CRT, sequential additional courses of FOLFOX after chemoradiation increased the pCR. Hence, a strategy utilising consolidation chemotherapy might offer more opportunity to avoid radical surgery [106].

More recent series of a 'watch-and-wait' strategy from Brazil have increased the RT dose and used extended courses of 5-fluorouracil and folinic acid following completion of chemoradiation with consolidation ('adjuvant') chemotherapy [49]. This strategy seems to be associated with higher rates of cCR. If patients undergoing CRT receive this consolidation chemotherapy, sequential PET/CT scans suggest that rectal cancers are less likely to regain metabolic activity in the short term (i.e. between 6 and 12 weeks [52•]). Whether this decreased metabolic activity extends for a longer term has not been investigated. Hence, the role of adding 'adjuvant' or maintenance chemotherapy after CRT either routinely or if a cCR is observed remains difficult to clarify.

What Is the Optimal Surveillance Programme/Follow-Up and How Long Should It Continue?

The present authors still have concerns that patients with initially curable cancers may be disadvantaged if surgery is not performed—either by local regrowth and the finding of extensive locoregional disease which cannot be salvaged by surgery, or by the persistence of irradiated but now resistant viable stem cells in the patient, which can increase the risk of metastatic disease. The greatest risk for recurrence appears to be within the first year after completion of CRT, hence follow-up should be regular, meticulous and rigorously performed during this period to ensure surgical salvage is feasible and timely.

The short follow-up <5 years in most studies and the few late recurrences previously reported by Habr Gama[39] suggest that these results may be premature. Following CRT and radical surgery in the German AIO study, 25% recurred locally after 5 years. More recent data provides a median follow-up of 60 months, which is reassuring [31]. Regrowth was observed in 31% of 90 patients, but only 4/28 had unresectable locoregional disease and only 5 developed metastases. Hence, a combination of serial clinical examination, endoscopy, MRI and CT imaging, as well as following the CEA trend—coupled with formal (in the sense that it happens) and regular MDT review (timing as agreed initially by MDT) of this data over a period of at least 7 years represents the best approach.

Long-Term Outcomes—Local Disease/Salvage Surgery/Risk of Unresectability/Risk of Metastases

Long-term outcomes from watch-and-wait are good—although there is a small proportion, where regrowth/recurrence is unresectable. Using a propensity score method to match and control for relevant features, a recent UK study suggests watch-and-wait after a complete clinical response is not inferior (and is perhaps even superior) to radical surgery in terms of overall survival in a matched population [69], although this study ignores the fact that a complete clinical response is in itself a good prognostic factor. Also it is possible that metastases are more common for those that experience a regrowth [62].

QOL Function After Watch-and-Wait

The effects of radiotherapy without any surgery on anorectal function have only been systematically studied in patients with anal or prostate cancer. Non-operative management following chemoradiation seems to result in better anorectal function compared with patients with near-complete response treated by transanal endoscopic microsurgery (TEM) [107]. The Dutch series reported good continence for patients managed by watch-and-wait in terms of Vaizey scores [29••].

The Future

Patients who reject radical surgery and the possibility of an attendant permanent stoma will often accept small but significant risks to avoid this. It is a different risk balance to actually recommend that all patients with small early T1/T2/T3a

cancers in the rectum should receive neoadjuvant CRT to avoid radical surgery. Patients with small early tumours would not invariably receive CRT and would usually proceed with primary surgery. With this, more inclusive strategy for delivery of CRT many patients are clearly exposed to the risks of long-term radiation unnecessarily as the majority will not obtain a pCR and will require definitive surgery.

If the MDT decision for CRT and a watch-and-wait strategy is made at the start, it should be recognised that surgical resection of the lymph nodes is not part of the planned management. This plan could then entail a higher radiation dose (to primary and elective nodes), a wider field size, the addition of brachytherapy or adjuvant chemotherapy—all of which may impact on long-term function and QOL. These alternative intensified and more effective neoadjuvant regimens could potentially increase complete tumour regression rates more consistently and have a major impact on outcomes of rectal cancer patients. Hence, these strategies need to be carefully audited, at the very least, and ideally investigated in prospective trials.

The International Watch &Wait Database (IWWD) http://iwwd.org/news/ is a prospective audit sponsored jointly by the Champalimaud Foundation, Portugal and the European Registry of Cancer Care (EURECCA) intended to capture patients with a cCR at 12 weeks following CRT, who undergo a non-operative strategy. We recommend clinicians support this initiative.

Conclusion

Although the evidence to support the feasibility and safety of watch-and-wait is accumulating in patients with small low early-stage rectal cancers, where clinical assessment is easier and simpler, the approach should not be extrapolated automatically and considered safe in more advanced cancers in the mid or upper rectum. In elderly and frail patients, radical surgery confers a high operative risk and there are clear benefits for avoiding surgery. However, there is a consistent 25–30% risk of locoregional tumour regrowth. Albeit this regrowth is usually endoluminal and can be usually salvaged by radical surgery, but the risk mandates close prolonged follow-up and even then approximately 6% may be unresectable and a few may develop metastatic disease. Furthermore, the safety of watch-and-wait if the initial tumour extends to the CRM and beyond (suggesting a multivisceral resection (MVR) is required) is uncertain. In such patients, nodal involvement is more common and extraluminal regrowth may be more likely. Also the ability to perform DRE may be compromised by a location high in the rectum.

Patients should be involved in the decision-making process, so a wider, more detailed evidence base is needed, which clearly provides the relevant information. Consensus-derived nationally approved guidelines and for watch-and-wait would facilitate informed discussions with patients.

At present, the data remains insufficient (only a few hundred patients worldwide and non-randomised) and consequently the balance of probabilities for benefit and harm are yet to be agreed and defined in a practical decision-making tree.

Compliance with Ethical Standards

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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