**Thinking through the multimodal treatment of localised oesophageal cancer: the point of view of the surgeon**

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**Abstract**

*Purpose of review:* This review examines current developments and controversies in the multimodal management of oesophageal cancer, with an emphasis on surgical dilemmas and outcomes from the surgeon’s perspective.

*Recent findings:* Despite the advancement of oncological neoadjuvant treatments, there is still no consensus on what regimen is superior. The majority of patients may still fail to respond to neoadjuvant therapy and suffer potential harm without any survival advantage as a result. In patients who do not respond, adjuvant therapy is still often recommended after surgery despite any evidence for its benefit. We examine the implications of different regimens and treatment approaches for both squamous cell cancer and adenocarcinoma of the oesophagus.

*Summary:* The efficacy of neoadjuvant treatment is highly variable and likely relates to variability of tumour biology. Ongoing work to identify responders, or optimise treatment on an individual patients, should increase the efficacy of multimodal therapy and improve patient outcomes.

*Keywords*: surgery, salvage, oesophagogastric, junctional, oesophagectomy, oesophagogastrectomy

**Introduction**

Combinations of radical surgery, chemotherapy and radiation therapy represent the modern approaches to the curative treatment of locally advanced oesophageal cancer, defined as clinical stage II or III (>cT3, N any, M0). Technical and scientific advances continue to increase therapeutic options, and increase the scope of discussion at multidisciplinary meetings.

There are myriad topics to consider. In this article, from a surgeon’s perspective, we have focused on key areas of current interest and relevance across the following domains:

1. Type of neoadjuvant therapy for adenocarcinoma of the oesophagus (OAC) and gastro-oesophageal junction
2. Neoadjuvant therapy plus surgery or definitive chemoradiation for squamous cell carcinoma (SCC)
3. The impact of radiotherapy dose and implications for salvage surgery
4. Surgery or surveillance after apparent clinical complete response (CCR) to neoadjuvant therapy
5. Adjuvant treatment after surgery
6. Novel therapeutic agents: Biologicals and immunotherapy
7. Tailored oncological treatment: Patient and tumour specific therapy

*Type of neoadjuvant therapy in adenocarcinoma of the oesophagus (OAC) and gastro-oesophageal junction (GOJA)*

The evolution of neoadjuvant therapy has historically been shaped by randomised clinical trials (RCTs) comparing neoadjuvant chemotherapy (NAC) or chemoradiotherapy (NACRT) plus surgery, to surgery alone. The seminal NAC RCTs included MAGIC, OEO2 and ACCORD, and the gold-standard NACRT trial was the Dutch multi-center CROSS RCT.1-4 While these trials have unequivocally shown the benefit of neoadjuvant therapy compared with surgery alone, the benefits of one regimen over the other, particularly in adenocarcinoma (AC), remains unclear at this time.

The recent publication of the German FLOT4 trial5 has seen a step change in selection of NAC for OAC. In this RCT of >cT1, N+, gastric and junctional (assessed according to the Siewert definition) adenocarcinoma, the addition of taxane therapy (docetaxel) to a regimen of fluorouracil, leucovorin, and oxaliplatin (FLOT), resulted in significantly improved response rates compared to a modified MAGIC regimen (ECF/ECX). Notable advantages included an increased rate of complete or subtotal tumour regression (37% vs. 23% p=0.02) and R0 resection rates (85% vs. 74%, p=0.02). A median survival of 50 months for FLOT compared to 35 months for ECF/ECX, with comparable toxicity profiles, has established a practice-changing regimen for gastric and junctional adenocarcinoma.

FLOT also represents a new challenge to CROSS-type NACRT (carboplatin and paclitaxel with concurrent 41.4 Gy radiotherapy) which has been the standard of care for OAC and GOJA for almost a decade in much of North America and continental Europe. Unlike historical NACRT regimens, CROSS is well tolerated with a low toxicity profile.6 NACRT moreover may downstage locally advanced disease and improve local control with approximately one in four patients with AC achieving a complete pathological response (CPR).7 However, 39% of patients with CPR in the CROSS trial relapsed, mainly at systemic sites.8 Numerous studies, including the POET and Neo-RES RCTs, as well as retrospective comparisons,9-13 have since reported that while increased rates of CPR and R0 resection are seen after NACRT compared to chemotherapy, these advantages do not necessarily translate into an appreciable difference in disease-free or overall survival. The reasons are unclear. One explanation for this may be that the reduced dose of systemic therapy given as part of the radio-sensitising element of CRT, whilst facilitating greater local down-staging, might potentially come at the cost of inferior systemic treatment. This remains a concern for proponents of neo-adjuvant chemotherapy despite some evidence of a modest systemic, as well as local, benefit seen in longitudinal follow up after CROSS.14

Accordingly, current RCTs are of great importance to address whether radiation therapy within the CROSS regimen has any advantage over the best chemotherapy only regimens. Several ongoing European trials (Table 1), including ESOPEC15 which compares CROSS vs FLOT, and Neo-AEGIS16, which compares CROSS with MAGIC or FLOT, are currently seeking to determine the optimal neo-adjuvant strategy for adenocarcinoma. Survival is the primary end point and will inform practice, particularly if consistent across all RCTs. Secondary end points will be of great importance, including toxicity, cost, and (of huge potential importance with regard to surgery) whether any differences in major postoperative morbidity and mortality are evident. Data on recurrence patterns will also give further insight into mechanisms of action and help explain any observed differences in survival.

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| **Table 1.** Current European trials comparing chemotherapy to chemoradiation in oesophago-gastric cancer | | | | | |
| **Study** | **Tumour type** | **Study arms** | **Recruitment target (n)** | **Study endpoint** | **Study status** |
| ESOPEC. German multicentre RCT | Oesophageal AC | FLOT vs. CROSS | 438, sample size calculated to detect 13% superiority of FLOT | 3y survival | Recruitment completed April 2020 |
| Neo-AEGIS. International multicentre RCT | Junctional or oesophageal AC | FLOT or ECF/X vs. CROSS | 540, sample size calculated to detect non-inferiority (10% margin) of the two regimens | 3y survival | Currently recruiting |

From a surgeon’s perspective, despite undoubted improvements in oncological therapies, only a minority of patients (20-50%) exhibit a response to neoadjuvant treatment for OAC (measured through clinical down-staging or histopathological tumour regression). Moreover, these patients cannot be predicted at the outset.5, 7, 17, 18 Current practice, regrettably, remains based on trials presenting an average reported survival benefit, when in fact this is not due to every patient gaining an incremental advantage. Rather, a select minority gain a large benefit and the remaining majority are exposed to neoadjuvant treatment and associated potential harm, without benefit to survival.17, 19 Given that neo-adjuvant therapy may reduce a given patients fitness by 20% or more before surgery,20-22 it remains difficult in contemporaneous practice to justify exposing all patients to toxic therapy when the majority will not benefit.

*Neoadjuvant therapy plus surgery or definitive chemoradiotherapy in squamous cell carcinoma (SCC)*

The increased sensitivity to CRT of SCC compared to AC has been well described. In the CROSS trial, a CPR in the resected specimen (no residual tumour cells, tumour regression grade 1) was seen in 49% of patients with SCC, compared to only 23% for AC patients.1 Clear surgical margins (R0) were obtained in 92% of patients overall following NACRT. Although the numbers randomised with SCC were small, at just 41 patients in the intervention group (23% of the total), these results have led to the adoption of neoadjuvant CRT as standard practice for the treatment of resectable mid- and lower oesophageal SCC, particularly in Western practice.

One issue that remains in question is the restrictive nature of the CROSS trial eligibility criteria, wherein patients were limited to age < 75 years, cT3 disease or less, and less than 10% weight loss, among others.7 TNM6 staging also meant that the degree of nodal disease burden was not considered. Studies assessing the applicability of CROSS outcomes to real-world practice have been mixed, as these patients, on average, are older with more comorbidity and more advanced disease than those in the original trial.23 In one study, fewer than 50% of treated patients would have met the original CROSS eligibility criteria and these patients had worse outcomes.24 However, other studies have shown similar outcomes in patients treated outside of a trial setting, albeit with a greater proportion of patients (90%) who would have met the trial eligibility criteria. Therefore, it remains unknown whether the promising results from the CROSS trial can be extrapolated to patients with more advanced local disease, particularly lymph node involvement, on a neo-adjuvant pathway.

The curative non-surgical alternative to NACRT in SCC is high dose RT, so-called definitive chemoradiotherapy (dCRT). In the UK, there are large regional variations in the use of dCRT versus NACRT for SCC, highlighting a lack of consensus in the published literature as to the best approach. Generally, the likelihood of selecting dCRT increases with more proximal tumours (particularly supra-carinal), the suspicion of local invasion, and poorer patient fitness. Whereas historically pharyngo-laryngo-oesophagectomy was performed for SCC of the cervical oesophagus, the high morbidity associated with the procedure, impact on patient quality of life, and the efficacy of alternatives in the form of dCRT means this is now rarely performed in Western patients.

The optimal treatment of mid- to lower-oesophageal SCC tumours, however, remains more controversial. A 2016 Cochrane review25 concluded that dCRT for SCC had equivalent outcomes to NACRT followed by surgery, although it acknowledged poor study quality and data heterogeneity. Non randomised trial comparisons have been flawed owing to inconsistencies in patient fitness, surgical resection standards and the inclusion of patients who had salvage surgery after dCRT. Two small RCTs26, 27 also showed no difference in outcome between dCRT and NACRT plus surgery, leading to a debate as to whether improvements in oncological therapy may have since tipped the balance in favour of an organ-preserving approach with dCRT.

Notwithstanding, one of the largest analyses to date, a 2020 retrospective population analysis of US data (n = 19,532) provided an important caveat. This analysis, which adjusted for patient factors through propensity score matching, found that survival of patients with SCC receiving dCRT was significantly inferior to those receiving NACRT followed by surgery (median 18.0 vs. 36.5 months, p < 0.001).28 Indeed other studies have confirmed better local control in patients undergoing surgery29, 30 and to date no high level data containing patients undergoing dCRT have matched the 60% 5-year survival seen in the NACRT arm of the CROSS trial. This uncertainty might easily justify a multi-centre randomised trial, however past efforts to recruit to such a trial were deemed futile, with just five patients recruited over a 3-year period,31 due to patient biases and the low incidence rates of SCC in Western practice. Subject to any level 1 evidence to the contrary, the consensus amongst surgeons, unsurprisingly, remains in favour of multi-modality therapy (including surgical resection) in fit patients with resectable mid- to lower-oesophageal SCC.

*The impact of radiotherapy dose and salvage surgery*

There has been widespread interest in the impact of radiotherapy dose on outcomes in both the neo-adjuvant and dCRT settings. In this context, several studies have suggested that “standard” RT doses used in NACRT are as efficacious as higher-dose regimens in achieving tumour downstaging. Studies by Ji and Ising, for instance, compared patients receiving 41.4Gy versus 50.4 Gy, including over 11,000 patients and found no differences in downstaging or CPR.18, 32 Ji et al additionally found that high-dose regimen patients suffered higher rates of post-operative mortality and reduced survival compared to low-dose regimens. Surgeons remain concerned by the higher postoperative complication rates associated with increased radiotherapy dose, particularly in the absence of any tangible survival or down-staging benefit. Consequently the 41.1 Gy as used in the CROSS regimen is the current standard in most countries, however 50.4Gy is still commonly applied in North America.

In the context of dCRT , the ARTDECO33 and PRODIGE 26 / CONCORDE34 trials have randomised patients to high or low dose radiotherapy (61.6 vs 50.4 Gy, and 76 vs 50 Gy, respectively). These have reported no difference in survival outcomes,33, 34 but with added toxicity (24% serious toxicity-related complications in high dose group, vs 16% in standard dose) following higher dose radiotherapy.33

In patients who undergo dCRT, so-called salvage surgery remains an option for patients with persistent or recurrent disease.35 The risks of surgery are increased in these cases, based on both a higher pre-operative radiation dose, and patient co-morbidities that may have precluded multimodal therapy in the first instance. As a result, mortality rates as high as 25% have been reported.36 Concerns also exist regarding the increased tissue fibrosis with the higher dose of radiotherapy (>55-60 Gy) typically given in dCRT, and the potential for greater complications, particularly to the lungs, heart and anastomosis. The high rates of anastomotic leak following increased doses of radiotherapy, which may affect the vulnerable microcirculation supplying the tip of the gastric conduit, is a concern for surgeons. A 2019 meta-analysis of 28 trials reported a relatively high overall rate of anastomotic leakage (18%) in patients who underwent salvage surgery,37 whilst a multi-centre European retrospective study reported significantly increased rates of anastomotic leak following dCRT followed by salvage surgery compared to surgery after standard NACRT (17.2% vs. 10.7%, p = 0.007).38 Anastomotic leaks increase post-operative mortality but also reduce long-term survival,39 a phenomenon which has been attributed to the increased activation of inflammatory cytokines and their effect on both immune function and cancer cells.40

In summary, salvage resection may provide a curative option in patients who have undergone dCRT, however the surgical risks are markedly increased. High dose RT and concerns regarding patient fitness, together combine to increase the risks in a patient population that already has minimal reserve to deal with complications. Those with proximal tumours are more challenging from a surgical perspective owing to the increased complications associated with upper mediastinal dissection and cervical (three field) lymphadenectomy41 as well as the lesser exposure of Western surgeons to high volumes of these cases.

*Surgery or surveillance after complete clinical response*

With the CROSS study reporting a CPR rate of 49% in SCC patients,8 there has been considerable interest in the potential to identify patients who might be “true” complete responders to CRT, and could forego standard surgery in favour of a more “as required” approach. Patients with a complete clinical response to neoadjuvant therapy, as determined by PET-CT, EUS, and endoscopy with bite-on-bite biopsies, may be suitable for surveillance rather than surgery as set out in the PreSANO study.42 This demonstrated an acceptable sensitivity (90%) for the detection of significant persistent or recurrent disease (>10% viable residual tumour cells ) following NACRT. Cohort studies and a systematic review have subsequently demonstrated a selective approach to be equivalent to standard surgery both in terms of post-operative outcomes and longer term survival.43-45 Approximately 30-50% of patients in the surveillance arms ultimately required surgery due to the detection of residual or recurrent disease, mostly within the first two years of monitoring.43, 45 Whilst there remain concerns about the potential to miss recurrent disease with this strategy, patient opinion would suggest this approach to be acceptable. In one scenario based questionnaire study, patients were prepared to accept a median reduction of 15% 5-year survival in order to potentially avoid surgery.46 Two major European trials, the French ESOSTRATE47 (AC only) and the Dutch SANO48 (AC and SCC), are currently underway to randomise patients with clinical complete response following NACRT to either routine care (oesophagectomy) versus intensive follow-up (multimodal imaging, endoscopy, and bite-on-bite biopsies) and surgery as required.

*Adjuvant treatment after surgery*

From a surgeons’ perspective, there are few areas in the management of locally advanced oesophageal cancer that provide as much controversy as the administration of postoperative chemotherapy to patients who are deconditioned after major surgery or may have suffered significant complications. An added consideration is the lack of high quality data underpinning this therapeutic decision. At this time, whether adjuvant therapy is planned after radical surgery is primarily determined by the regimen chosen, with FLOT or ECX incorporating post-operative treatment cycles, whereas no adjuvant therapy is prescribed following CROSS. The specific benefits afforded by the adjuvant component of treatment are unknown. Given the severity of the operative insult, it is not surprising that in RCTs less than 50% of patients received the full allocation of post-operative chemotherapy due to the accumulation of acquired therapeutic toxicities.2, 5

A further source of contention is the administration of adjuvant chemotherapy in the context of an individual patient’s response to neo-adjuvant treatment. A pertinent question in the responder group is whether the majority of the benefit has already been afforded by the pre-operative component of treatment. Conversely, in non-responders, the continued administration of the same combination of toxic drugs that have already proven to be ineffective by radiological or pathological criteria seems difficult to justify in the modern era. In the FLOT 4 trial for instance, despite the encouraging survival, only a minority (37%) of patients showed significant histological tumour regression.5 In the absence of high level data, multi-disciplinary teams are left to question whether pathological tumour regression provides a definitive answer as to whether a patient has responded to chemotherapy or whether other surrogates such as radiological down-staging or lymph node response should be taken into account when justifying the decision to complete adjuvant therapy. This conspicuous gap in the evidence base needs to be addressed by prospective studies.

Pending this, the results of cohort studies and meta-analyses have provided the only available data. For patients on a peri-operative chemotherapy pathway, these suggest some benefit for adjuvant chemotherapy in patients who were pathological responders to NAC, which seems logical.17 Following NAC, a number of studies have suggested adjuvant chemoradiotherapy instead to be beneficial in lymph node and/or margin positive patients.49, 50 Interestingly, in one large cohort study, this benefit for CRT was most pronounced in non-responders to NAC, implying that a change in strategy might be beneficial for these patients.49 Following NACRT, a review of the national cancer dataset in the USA using propensity matched analysis, revealed a survival benefit for adjuvant chemotherapy compared to no adjuvant treatment in adenocarcinoma, albeit with only a small proportion of patients (<10%) undergoing adjuvant therapy overall and the obvious issue of confounding.51

*Novel therapeutic agents: Biological agents and immunotherapy*

The addition of targeted therapies including growth factor receptors or immunotherapy represents a new class of oncological therapy that has been studied predominantly in metastatic disease. These work by targeting key cell receptors, or their ligands, involved in the tumour progression pathway.

In locally advanced disease, the ST03 trial randomised patients with adenocarcinoma of the stomach, junction or oesophagus to neoadjuvant ECX with or without bevacixumab, an anti-VEGF-A monoclonal antibody. No difference in long term survival outcomes was evident.52 Crucially, the finding that anastomotic leak rates were more than twice as common in the intervention group (24% vs. 10%) led to late-stage trial recruitment being abandoned for the oesophageal cohort, and has fuelled concerns about the effect of such agents on postoperative complications.53

The PD-1 receptor and its ligand PD-L1 has emerged as a promising target for a range of cancers, including those of gastric and oesophageal origin. The activation of PD-1 expressed on T-cells has an inhibitory effect on immune response by those cells. Anti-PD-L1 agents, therefore, inhibit this action and “reactivate” the immune system against the PD-L1-expressing tumour cells. Microsatellite instability (MSI), the presence of short-chain repeated DNA sequences accrued through DNA mismatch repair, is known to be associated with PDL-1 expression by tumour cells, and is predictive of response to anti-PD-1 therapy.54

A recent abstract has reported positive early outcomes in the Checkmate 577 trial which if confirmed in published data has the potential to change practice.55 In this trial, patients with stage II/III oesophageal or junctional cancer received NACRT prior to surgery, and patients with incomplete pathological responses were randomised to the anti-PD1 inhibitor nivolumab or placebo. Disease free survival was significantly improved (HR 0.69, median DFS 22.4 vs 11.0 months) with nivolumab. The results of several ongoing early trials for the use of other agents including pembrolizumab, tremelimumab (CTLA-4 antibody), and durvalumab (PD-L1) as part of primary neoadjuvant treatment regimens, are awaited.

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| **Table 2.** Selected examples of current evidence for monoclonal antibody agents in oesophageal cancer | | | |
| **Associated receptor target** | **Agent** | **Study** | **Results** |
| HER2 | Trastuzumab, pertuzumab | Innovation RCT56 | Ongoing trial of neoadjuvant chemotherapy vs. chemotherapy + trastuzumab vs. chemotherapy + trastuzumab + pertuzumab. |
| VEGF | Bevacixumab | ST03 RCT52 | No difference in outcomes when added to ECX. Possibly increased complication rates led to late trial recruitment stoppage. |
| PD1 | Nivolumab | CheckMate 57755 | Adjuvant nivolumab following NACRT and surgery superior to placebo with doubling of DFS (abstract published only). |
| EGFR | Panitumumab | Patient-derived organoid model57 | Paradoxical increase in tumour cell viability with panitumumab. |

*Tailored oncological treatment: Patient and tumour specific therapy*

The fact that many patients do not derive any benefit from neoadjuvant therapy continues to drive efforts to identify this groupas early as possible in the treatment pathway. Some general trends are increasingly recognised and may shape therapeutic decisions such as the reduced effectiveness of standard chemotherapy in signet ring cell tumours and those exhibiting MSI.58, 59 “Personalised” or “precision” medicine, or “tailored” therapies, describe strategies which aim to reliably predict the most effective treatments for individual patients based on variables such as tumour biology, tumour cell receptor expression, or genome sequencing. The heterogenous nature of oesophageal tumours is both the reason that the current standardised treatment approach is not applicable to all patients, but also why identifying reliable targets has proven difficult. Research is currently at an early stage with early-phase trials investigating individual receptor targets.56, 60 Wider pragmatic clinical trials of tailored therapy have been proposed but these have not progressed beyond a developmental stage.61

In the absence of patient-specific agents, modifications to treatment after standard induction neoadjuvant treatment, with an assessment of disease response remains the next best option. Typically, this assessment is performed using PET-CT, with the most commonly accepted definition of a significant response being a reduction in SUVmax of at least 35%.62, 63 While it is well recognised that differing tumour biology means that some patients may be classed as “responders” and others “non-responders,” reliably identifying these patients on imaging, as well as deciding what to do with non-responders, has remained challenging. Previous trials such as the MUNICON series63, 64 have demonstrated the feasibility of attempting such an approach, but have not been able to identify a management algorithm to improve survival for non-responders.

More recently, the Alliance trial65 randomised patients with AC to a modified FOLFOX or CROSS chemotherapy, plus concurrent radiotherapy. Following reassessment after the first round of therapy, PET-adjudged non-responders were crossed over to the other treatment arm. Despite this, non-responders still performed significantly worse than responders (median 40.2 vs. 27.4 months). Greally et al recently reported one of the few studies to explicitly assess the effect of tailoring in non-responders,66 in a retrospective study comparing non-responders who either continued with first-line NACRT, or changed to second-line chemotherapy agents as part of a tailored NACRT regimen. In this small series (41 non-responders), changing chemotherapy did not have an effect on survival (14.1 months for those who changed versus 17.2 months for those who did not, p = 0.81). While a prospective trial randomising non-responders to tailored versus standard therapy would provide a more definitive answer, concerns regarding the reliability of PET-CT or other imaging modalities to identify responders, and the absence of any reliable bio-markers of response, represent on-going challenges.

Recognising the complexity of the underlying biology, artificial intelligence driven approaches may allow better integration of varied, complex and sometimes abstract data.67 Neural networks have shown promise in early studies, allowing greater precision in pre-treatment prediction of response with both gene expression68 and PET-CT69 derived features. Automated neural network analysis of diagnostic biopsies to identify abstract features predictive of response has been demonstrated in rectal cancer,70 and work to replicate this in oesophageal adenocarcinoma is underway. These studies are all limited by sample size, however solutions that maximise the utility of imaging and histopathology in particular are attractive as they utilise routinely collected data (as opposed to genomics), which can be more easily scaled for both validation and widespread uptake.

*Conclusion*

Modern oncological agents, medical and surgical care, and an improved understanding of oesophageal cancer biology now offer greater treatment options than ever before to patients who might otherwise face a very poor prognosis. International trends encouragingly show improved outcomes. The availability of such options, however, serves also to highlight the lack of consensus on what should constitute gold standard treatment, and whether this term in itself becomes redundant in an era of individualised therapy. Some of the many trials currently ongoing may help to shed light on this. Undoubtedly, a multidisciplinary and collaborative approach to the treatment of patients with oesophageal cancer will continue to be the keystone of care. Surgeons have long since accepted the importance of combining effective local and systemic therapy in order to treat the overall disease burden and improve outcomes in these patients, but without adding unacceptable post-operative risks. The surgeon’s role at the core of the oesophageal cancer MDT is accordingly increased rather than diminished in the modern era.

**Key points**

* The benefit of neoadjuvant chemotherapy versus chemoradiotherapy in adenocarcinoma is the subject of several ongoing randomised trials
* Large database analyses suggest that SCC may be best treated with neoadjuvant chemoradiation (nCRT) and surgery, rather than definitive chemoradiation (dCRT)
* Salvage surgery in patients who have higher-dose dCRT with recurrent or persistent disease are at potentially greater risk of complications compared to nCRT
* The majority of patients fail to respond to chemotherapeutic treatments, potentially suffering harm without survival benefit. Work towards better identifying responders, and tailoring therapy to individual patients and tumours, is ongoing.

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Randomised trial reporting no difference in survival outcomes for high versus low dose radiation in chemoradiotherapy treatment of SCC, currently abstract published only.

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