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The Role of Adjuvant Treatment in Resected T3N0 Rectal Cancer

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Abstract Since the adoption of total meso-rectal excision as the standard surgical approach for management of locally advanced rectal cancer, there has been a significant reduction in local recurrence. Neoadjuvant combined modality treatment with 5-fluorouracil-based chemotherapy and radiation has further improved local disease control and overall survival. Given the excellent survival obtained with this combined approach in T3N0 rectal cancer, there are concerns about the need for further exposure to chemotherapy with unproven benefit. We review the evidence for adjuvant chemotherapy in this setting and set out clinico-pathologic variables that may be useful for making a decision in favor of offering adjuvant therapy or observation.

Keywords T3N0 · Stage IIA rectal cancer · Locally advanced · Chemotherapy · Adjuvant · Neoadjuvant · Total meso-rectal excision · Combined modality treatment · Complete response · Watchful waiting

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Introduction

Surgery remains the primary curative option for rectal cancer, and in the twenty-first century, total meso-rectal excision (TME) is the standard surgical approach. This involves complete removal of the tumor with excision of the mesentery around the involved rectal tissue to allow sufficient lymphatic vasculature and lymph node retrieval [1, 2]. The widespread adoption of TME is central to the improved outcomes seen in the last few decades in locally advanced rectal cancer with both improvements in local recurrence and cancer-related survival [3]. Adjuvant therapy is often employed for control of metastasis, and at the end of the last century, adjuvant therapy, initially as radiation therapy, but later offered in a combined modality treatment approach (CMT) of 5-fluorouracil (5-FU)-based chemotherapy, and concurrent radiotherapy was adopted in the USA and many European countries as standard management for stages II and III rectal cancer. This followed from several studies in the preceding decades that established the superiority of this approach to standard surgery only [4, 5].

There has however been a number of practice-changing ideas since the National Institute of Health's (NIH) consensus statement recommending adjuvant treatment in stages II and III colorectal cancer [6]. Key among these is the growing recognition that stage II colon and rectal cancers are clinically distinct from stage III cancer and may not derive similar benefits from adjuvant therapy. As it stands today, the optimal approach to the management of stage IIA rectal cancer, where the tumor has invaded into the perirectal tissues, but not the peritoneum or lymph nodes (T3N0) in the adjuvant setting remains controversial. This has been considered "intermediate-risk disease" [7], and the controversies surround whether all patients should receive adjuvant therapy and defining the population that would benefit from such therapy [8]. In those who require adjuvant therapy, the optimal treatment agents in

have also not been well defined. The aim of this review is to contribute to the debate by reviewing the evidence for adjuvant chemotherapy in T3N0 rectal cancer. We will also document data that have accrued over the last decade that may assist the medical oncologist in making decisions about adjuvant treatment.

CMT for Locally Advanced Rectal Cancer: How the Standard of Care Has Evolved

By the end of the last century, it was clear that combined modality treatment was superior to surgical treatment alone for locally advanced rectal cancer (LARC). The North Central Cancer Treatment Group (NCCTG) reported a reduction in local recurrence and distant metastasis in patients treated with adjuvant chemoradiation (5-FU, semustine, and 45-Gy radiation with 5.4-Gy boost) compared to adjuvant radiation only, which was the standard of care at the time. They also reported a significant survival benefit, with death rates over 7 years of follow-up reduced by 29 % (62/100 vs 49/104, $P = 0.043$), favoring the combined modality group [5]. This followed on from a four-arm adjuvant trial, where patients were randomized to observation, radiation, chemotherapy only or combination chemotherapy using 5-FU and semustine, and radiation treatment carried out by the Gastrointestinal Tumor Study Group (GITSG). This group reported significantly improved disease-free survival with the combined modality approach, although there was no evidence of a difference in overall survival [9]. These studies informed the National Institutes of Health consensus recommendation for adjuvant chemoradiation in stages II and III rectal cancer [6]. The National Surgical Adjuvant Breast and Bowel Project (NSABP)-R02 trial provided further evidence that radiation was a vital part of the combination with improved local recurrence rate 13 vs 8 %, $P = 0.02$, although that study did not show a survival benefit [10]. It is therefore not surprising that until 10 years ago, the prevalent practice in the management of LARC was adjuvant chemoradiation [11]. However, in the years since the above publication, a number of studies have established the favorability of neoadjuvant therapy over adjuvant therapy, making this the present standard of care.

Two studies from the USA, the Intergroup (INT) study 0147 and the NSABP-R03, were designed to compare the roles of neoadjuvant and adjuvant chemoradiation in locally advanced rectal cancer. These studies closed early due to poor patient accrual. The German CAO/ARO/A10 [12, 13] had similar objectives with end points of overall survival, local recurrence (LR), and disease-free survival. Significantly, and in contrast to prior studies in stages II and III rectal cancer, this study utilized TME as the surgical approach for the 647 patients that were randomized. Local recurrence rate was reduced by about 50 % in the neoadjuvant arm at 6 % compared to 13 % in those who received CMT in the postoperative setting. Also, early and delayed toxicities were reduced in the preoperative CMT arm compared to the postoperative arm, although the patients in the latter arm received a 10 % higher total dose of radiation. However, there was no significant difference in median or 5-year overall survival (76 vs 74 %, $P = 0.8$). Regardless, given the improvement in local control and the more tolerable adverse effect profile, neoadjuvant combined therapy is the current standard in the USA and many parts of Europe [14]. An update of the NSABP-R03 trial reported improved pathologic complete response without a difference in local recurrence rate of 11 %. Importantly, the trial showed for the first time an improvement in disease-free survival (DFS) with a trend towards improved overall survival (OS) in patients who received neoadjuvant CMT [15]. The neoadjuvant approach in the above studies included up to 50 Gy of radiation concurrent with infusion 5-FU-based chemotherapy prior to surgical resection. Subsequent trials established the superiority of infusion 5-FU over bolus 5-FU [16, 17]. In addition, the NSABP-R04 study showed that capecitabine is of equivalent efficacy to 5-FU in this setting [18] in concordance with reports out of Europe [19]. As such, capecitabine is widely substituted for 5-FU in neoadjuvant CMT.

What Is Known About T3N0 Rectal Cancer?

The studies described in the previous sections involved patients with stages II and III LARC. This is a basket that contains distinct pathologic entities, including tumors extending outside the rectal wall and those that carry nodal metastasis. Clearly, these entities differ in risk, as nodal metastasis and more advanced tumor (*T*) categories carry different prognosis. For example, a retrospective study reported a 10-year recurrence-free survival of 87 % in T3N0 rectal cancer in the absence of poor-risk pathologic features following surgical excision alone [20]. The Intergroup 0114 study identified T3N0 rectal cancer as low risk based on a significant difference in disease recurrence-free rates, DFS, and OS in this cohort compared to T3N+ or T4 disease [21]. The authors commented that in the absence of other high-risk features, adjuvant radiation might not be required in this setting. In a combined analysis of multiple trials spanning at least a decade (preceding the widespread adoption of neoadjuvant therapy), Gundersen and colleagues categorized T3N0 tumors as "intermediate risk" with described OS of 75 % compared to 65 % for T4 tumors. They also described better 5-year DFS, LR, and rate of distant metastases [7]. The argument has thus been made that medical and radiation oncologists may be over-treating patients with T3N0 tumors with combined modality treatment either in the adjuvant or neoadjuvant setting, particularly in the TME era. Indeed, the Dutch TME trial found that preoperative radiotherapy was most beneficial in node positive disease [22]. The

opposite side of that argument is that up to 30 % of clinically diagnosed T3N0 rectal cancer (cT3N0) may have nodal involvement following resection [23]. As such, some would contend that over-treatment is less risky than under-treatment for clinically staged cT3N0 rectal cancers. For the most part, this argument really only justifies the incorporation of neoadjuvant CMT in the management of cT3N0 rectal cancer but does not address the use of postoperative chemotherapy at all. Similar to stage II colon cancer, we are therefore compelled to examine more closely the role of postoperative treatment in T3N0 rectal cancer.

Adjuvant Therapy Following Neoadjuvant CMT

The German Rectal Cancer Study Group's CAO/ARO/AIO-94 trial laid the foundation for neoadjuvant combined modality treatment as the standard approach to the management of stages II and III rectal cancer. Only 29 % of patients in this trial had stage II disease. Patients in the neoadjuvant CMT arm received 4 cycles of 5-FU-based chemotherapy postsurgery [12, 13]. Other studies in this setting follow a similar approach and have shown similar results [24], and the National Comprehensive Cancer Network (NCCN) guidelines currently recommend adjuvant fluorouracil, leucovorin, and oxaliplatin (FOLFOX) in this setting [25]. While the rationale-reduced distant metastasis- for "consolidation" adjuvant chemotherapy is sound, the clinical evidence in support of the practice remains remarkably thin, particularly for stage IIA rectal cancer (T3N0). A 2012 Cochrane review reported a 17 % reduction in overall survival with adjuvant chemotherapy compared to observation (HR 0.83, CI 0.76–0.91). However, there was moderate but significant heterogeneity ($P = 0.03$) between studies. A number of the studies were completed prior to widespread adoption of TME or neoadjuvant chemotherapy [26].

The European Organization for Research and Treatment of Cancer (EORTC) trial 22921 is the largest study to directly investigate the role of postoperative chemotherapy following preoperative CMT or radiotherapy. This somewhat controversial study randomized 1011 patients into 4 arms consisting of neoadjuvant radiotherapy followed by adjuvant chemotherapy, neoadjuvant CMT, and then adjuvant chemotherapy; preoperative radiotherapy followed by observation; and neoadjuvant CMT followed by observation. While patients who received neoadjuvant CMT did better overall in terms of local disease recurrence in line with the current knowledge, there was no evidence of a significantly improved disease-free survival (5-year DFS 51.8 vs 48.4 %, HR 0.91, $P = 0.32$) or overall survival in the cohort who received adjuvant chemotherapy (5-year OS 47 vs 43 %, HR 0.91, $P = 0.29$) compared to observation [27••, 28••]. Adjuvant therapy did not significantly alter the 10-year rates for distant metastasis. The reservations about this trial include the lower doses of 5-FU administered in the adjuvant setting compared to what is standard practice in the USA. Also, more than 50 % of the patients did not receive adjuvant chemotherapy as planned. While these are valid criticisms, the latter point mirrors what happens in actual clinical practice, where after radiation and surgery, many patients are unable to complete a full course of adjuvant chemotherapy.

The PROCTOR-SCRIPT trial is a smaller study by the Dutch Colorectal Cancer Group that attempted to answer the same question, with adjuvant chemotherapy administered as 5-FU or capecitabine. Although the study closed early due to slow accrual, among the 437 eligible patients, 216 were randomized to the adjuvant chemotherapy arm following neoadjuvant CMT vs 221 in the observation arm. There was no meaningful difference in loco-regional recurrence (7.8 %) and distant metastasis (38.7 vs 34.5 %, $P = 0.29$). More importantly, there was no significant difference in 5-year OS (79.2 vs 80.4 %, HR 0.93, $P = 0.73$). In addition to the small sample size, a criticism of this study is the dosing regimen of 5-FU employed (375-mg/m^2 bolus), which may be more toxic and less effective than continuous infusion regimens or capecitabine [29••]. The Italian National Research Council has also compared adjuvant 5-FU and leucovorin to observation following neoadjuvant CMT. Of the patients, 28 % did not receive adjuvant chemotherapy as planned, but overall, there was no difference in local failure, distant metastasis, disease-free survival, and 5-year OS with adjuvant chemotherapy [30•].

The addition of oxaliplatin to 5-FU in the postoperative setting is also controversial for stages II and III rectal cancer. The CHRONICLE study was closed because of slow accrual, with less than 50 % of patients completing adjuvant capecitabine and oxaliplatin. Although the number enrolled was small (113), there was no significant difference in disease-free and overall survival [31•]; in addition, up to 40 % grades III and IV toxicities were reported. Based on the evidence above and others [32], there is insufficient evidence to support the use of adjuvant 5-FU-based chemotherapy following preoperative CMT and TME in LARC generally and almost certainly in T3N0 cancer [33]. It is difficult even within clinical trial settings to ensure patient compliance, there is added toxicity and there is no survival benefit reported. Based on this lack of evidence, the Second European Rectal Cancer Consensus was unable to make a firm recommendation about the benefit of adjuvant chemotherapy following CMT [34].

Despite the lack of convincing evidence for adjuvant chemotherapy following surgical excision, the relatively small phase II ADORE trial described better 3-year disease-free survival with the use of FOLFOX compared to 5-FU [35•]. Pertinent to this discussion, patients with stage III disease largely drove this benefit, as there was no difference in DFS between either arm in patients with stage II disease. Similarly, the German Colorectal Cancer Study Group reported

improved disease-free survival with combination of 5-FU and oxaliplatin, 75.9 vs 71.2 % ($P = 0.03$), but there was no difference in 3-year overall survival, which was remarkably high at 88 % [36••].

Given that T3N0 rectal cancer has been considered low- to intermediate-risk disease, one could argue that patients with this stage of rectal cancer may do well without adjuvant therapy. The beam of management and research should therefore be aimed at identifying the subset of patients who may require adjuvant treatment. This becomes more important, as outside of clinical trials, a good number of oncologist may not be eager to offer adjuvant treatment to patients with stage II rectal cancer [37] and less than 50 % of patients may actually receive adjuvant therapy when initially planned, largely due to toxicities [38, 39].

Adjuvant Treatment Without Prior Neoadjuvant Therapy

Despite the accuracy of modern high-resolution MRI [40], there remains a significant challenge of under-staging, as up to 20–30 % of clinically node-negative disease cT3N0 may have metastatic disease involving the lymph nodes following surgery and pathology evaluation [41]. This has implications for further treatment and provides the most compelling rationale for neoadjuvant treatment. In the absence of prior preoperative treatment, the questions that arise are whether patients who are upstaged following surgery should be offered postoperative chemotherapy or CMT. With TME, low LR is the norm so the over-riding goal is to reduce systemic recurrence.

The Quick and Simple and Reliable (QUASAR) trial, a large multi-national trial randomized about 3200 patients with node-negative colon and rectal cancer to observation vs adjuvant 5-FU and folinic acid. About 20 % of the patients in each arm had rectal cancer. The study reported a small absolute survival benefit of 3.6 % with adjuvant therapy in colorectal cancer. In the subgroup of patients with stage II rectal cancer, adjuvant therapy resulted in a significant reduction in risk of disease recurrence within the first 2 years (8.5 vs 14.7 %, $P = 0.007$). This benefit did not, however, translate to a survival advantage ($P = 0.05$) [42]. Sakamoto and colleagues in a meta-analysis of five trials comparing postoperative fluoropyrimidine-based treatments (including uracil-tegafur) with observation reported a small 5 % survival benefit over observation alone [43], and more recently, the oral fluoropyrimidine S-1, which is a combination drug of tegafur, gimeracil, and oteracil potassium, was judged to be superior to uracil-tegafur on the basis of improved relapse-free survival. Again, there was no overall survival benefit noted [44]. Wu et al. in a single institution study of 141 patients with pT3N0 rectal cancer described similar OS and disease-free survival among patients who received adjuvant 5-FU-based chemotherapy and adjuvant chemoradiation after TME [45]. Interestingly, patients who received adjuvant CMT had lower 5-year OS at 72.4 compared to 83.3 % in the adjuvant chemotherapy-only group, which may reflect selection bias with the over-representation of poorer risk low-lying tumors in the smaller (<30 % of total sample) CMT group. Of note, Merchant reported overall survival of 75 % with TME alone in T3N0 rectal cancer [46]. The QUASAR study therefore provides the best-quality evidence for recommending adjuvant chemotherapy in T3N0 rectal cancer, although the benefit described is small. Despite a paucity of data, the NCCN, primarily based on extrapolation of data from the MOSAIC trial [47], recommends adjuvant FOLFOX with stages II and III rectal cancer. Some other experts offer 4–6 months of 5-FU or capecitabine alone in this setting.

Risk-Adapted Management of T3N0 Rectal Cancer

In addition to poor compliance with adjuvant treatment, the inconsistent demonstration of a survival benefit reported with the addition of adjuvant chemotherapy following neoadjuvant CMT and surgical resection likely reflects the clinical and pathologic heterogeneities of T3N0 rectal cancer. Nodal involvement, lymphovascular invasion (LVI), and disease involvement of the circumferential margins (CRMs) have been established as risk factors for disease recurrence and inferior survival in this patient population [40, 48]. In addition, others have published on this topic. For example, the College of American Pathologists has published prognostic and predictive criteria useful for risk stratification in colorectal cancer [49]. These criteria have informed a more nuanced approach to management of stage II colon cancer. More specifically for rectal cancer, the presence of low-lying tumors, historically (but inconsistently) described as within 5 cm of the anal verge, is regarded as a poor prognostic indicator [50], and such tumors may be more likely than more proximally placed tumors to respond to chemoradiation [51]. Investigators at the Memorial Sloan Kettering Cancer Center identified LVI, preclinical carcinoembryonic antigen >5 ng/ml, and age greater than 70 years as important indicators of outcomes, including local recurrence and overall survival following TME in a review of 100 patients with T2-T3N0 rectal cancer who received surgery alone [52]. Similar findings were previously reported from the Massachusetts General Hospital with 10-year recurrence-free survival of 87 % in patients with favorable, well to moderately differentiated histology, absence of lymphovascular invasion, and minimal <2-mm tumor invasion of the perirectal fat, compared to 55 % in patients with less favorable histology based on the above [20]. As with stage II colon cancer, it is reasonable to incorporate these clinico-pathologic findings into the decision-making algorithm for management of T3N0 rectal cancer. In our view, patients who do not exhibit high-risk features may forego adjuvant chemotherapy.

Gene-based recurrence scoring models may be useful in defining prognosis and dictating the need for adjuvant therapy. A 12-gene colon cancer recurrence scoring system has been validated in stages II and III rectal cancer in the Dutch TME trial, with a greater discriminant effect reported for stage II rectal cancer [53]. The model has not been embraced in clinical practice even for colon cancer, but it may be worth exploring particularly in the patient population being reviewed.

Pathologic staging based on complete response (CR) rates following neoadjuvant therapy is a widely recognized indicator of prognosis. Pathologic CR (pCR) has been described in up to 25 % of locally advanced rectal cancer following neoadjuvant CMT [54]. An Italian group reported a LR rate of 1.6 % in a large series of patients who attained a pCR following neoadjuvant CRT [55]. Also, among 725 patients with stages II and III rectal cancer, Park and colleagues reported an 18 % pCR rate with a 5-year OS of 93.4 compared to 77.3 % for poor responders ($P = 0.002$) [56]. Maas and colleagues also reported a 5-year metastasis-free survival of 89 % in patients who achieved a pCR vs 75 % ($P < 0.0001$) in those who did not in a meta-analysis [54]. Finally, Valentini and colleagues emphasized the role of pathologic CR in the development of a normogram designed to aid decisions about adjuvant chemotherapy in LARC [57]. Even a less strict, greater than 95 % CR rate has been associated with significantly improved 5-year overall survival of 93 % compared to 66 % ($P < 0.003$) in a cohort with less than 95 % CR [58], although a more recent study from the Netherlands, while confirming the survival benefit with a CR, did not report a benefit with near CR [59]. These findings have spurred efforts to improve pathologic response with newer combinations of chemotherapy. The STAR-01 trial evaluated the role of oxaliplatin and infusion 5-FU with radiation in locally advanced rectal cancer. The rate of pCR with this regimen was 16 % similar to what was obtained with the 5-FU and radiation arm. There were increased grades 3 and 4 adverse events in the oxaliplatin arm [60]. The ACCORD-Prodige 2 trial reported similar findings, discouraging the addition of oxaliplatin in the neoadjuvant setting [61]. Given the remarkably long-term survival with a pCR following neoadjuvant therapy, this would be a reasonable marker for determining the need for adjuvant chemotherapy as argued by Park et al. [56]. In line with this, a small retrospective study suggested that adjuvant 5-FU-based chemotherapy might not be beneficial in patients who achieved successful downstaging to ypN0 [62], and Capirci and colleagues were also unable to uncover a benefit for adjuvant 5-FU in 566 patients with pCR after neoadjuvant CMT and radiation [55]. On the contrary, an ad hoc analysis of a group of patients in the EORTC 22921 trial offers a dissenting position, suggesting a significant, albeit small survival benefit [63] for adjuvant therapy in patients with complete to partial response (ypT0-T2), while those with less impressive response ypT3-T4 did not seem to benefit. This is significantly different from results in other studies in this area, and it may be related to the heterogeneity of the ypT0-T2 group with complete and partial responders lumped together with the additional benefit of adjuvant therapy in this group possibly being due to the presence of partial responders.

Future Perspectives: Lessons from Anal Cancer

Nonsurgical management is now the accepted practice for the management of anal cancer due to significant complete response obtained with combined modality treatment with chemotherapy and radiation [64], and there is a suggestion that this may be applicable to rectal cancer in the future. Following pioneering work from Brazil [65], there is enthusiasm for watchful waiting following neoadjuvant chemoradiation in patients who achieve a complete clinical response (cCR). In addition to sparing patients adjuvant chemotherapy, this approach also eliminates surgical excision with the potential morbidity including sphincter-associated complications and colostomy. In a 2014 study, Habr-Gama and colleagues reported their experience with 183 patients with LARC. Close to 50 % of patients achieved a cCR after a 5-FU-based CMT regimen similar to standard practice in the USA, with 19 % showing early recurrence. After a median follow-up of 5 years, they reported a 69 % LR-free survival and a 5-year cancer-specific survival of 91 %, suggesting that salvage was achieved with disease recurrence [66••]. More recently, investigators from Denmark offered CMT to 51 patients with LARC. In this single-arm prospective study, CMT consisted of 60-Gy radiation to the primary tumor and 5-Gy endorectal brachytherapy with concurrent tegafur-uracil. This high-dose regimen was reported to be tolerable with acute grade 3 diarrhea reported in 8 % of patients and delayed grade 3 rectal bleeding reported in 17 % of patients. cCR was about 80 % and LR in this group at 1 year was 15 % [67]. These studies suggest that in a cohort of patients who achieve a cCR with upfront CMT, watchful waiting may be considered. However, larger collaborative studies will need to be performed likely as retrospective pooled analysis to determine the place of this approach in management of patients with T3N0 rectal cancer. Importantly, the definition of complete response has to be harmonized and patients have to be aware of the need for routine and regular digital rectal examinations (DREs), MRI, and proctoscopy with biopsy if this approach is offered.

Conclusion

The optimal management of T3N0 rectal cancer remains controversial with a key driver of this controversy being the role of adjuvant chemotherapy. Where decisions have been made, whether per the oncologist's expertise or based on guideline recommendations to offer adjuvant chemotherapy, the optimal

agent or combination of agents has not been fully decided. Patients with T3N0 rectal cancer have the opportunity to be offered "personalized treatment." Given the impressive disease control that has been achieved with neoadjuvant combined modality treatment and TME in stage II rectal cancer patients, there is a strong case to be made for adoption of observation in patients who are unwilling or unable to tolerate adjuvant chemotherapy. Indeed, the weight of the evidence is in support of this practice [33]. For practitioners who are uncomfortable excluding postoperative chemotherapy, or in cases where adverse clinical risk factors such as LVI are present, we would argue that combination therapy is likely overtreatment and would advocate for single-agent fluoropyrimidine therapy in these patients. In the years ahead, more patients with cT3N0 rectal tumor may be able to avoid surgery altogether if they achieve a rigorously defined complete clinical response with CMT.

Compliance with Ethical Standards

Conflict of Interest Olumide B. Gbolahan declares that he has no conflict of interest. Bert O'Neil has received compensation from Amgen and Genentech for service as a consultant.

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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