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Colorectal Cancer: Postoperative Adjuvant Therapy

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Key Concepts

- Patients with stage III colon cancer should be considered for adjuvant chemotherapy.
- Oxaliplatin-based adjuvant chemotherapy regimens improve survival of stage III colon cancer patients by an absolute 20–25 % at 5 years versus no chemotherapy.
- Adjuvant chemotherapy has not been demonstrated to have significant impact on survival for stage II colon cancer patients, but it can be considered for patients whose tumors have high-risk features.
- In colon cancer patients, radiotherapy should be considered when tumors penetrate other fixed structures (T4) and can be guided by placing surgical clips at the time of operation.
- Patients with clinical stage II and III rectal cancers who undergo neoadjuvant chemoradiotherapy should be considered for postoperative adjuvant chemotherapy, regardless of the final pathologic staging, although the efficacy of adjuvant chemotherapy in this setting has not been firmly established.

While surgery remains the primary treatment for patients with colon and rectal cancer, adjuvant treatment with chemotherapy and radiotherapy plays an increasingly important role. For patients with stage III colon cancer, adjuvant chemotherapy has been recommended since 1990 [1]. More recently the National Quality Forum has endorsed metrics related to the administration of chemotherapy in stage III colon cancer patients in order to ensure that patients with stage III colon cancer not only are considered for chemotherapy but are given chemotherapy in a timely fashion [2]. For patients with stage I colon cancer, surgery alone is highly successful, and thus no adjuvant therapy is currently recommended. On the other hand, patients with stage II colon cancer may benefit from adjuvant treatment, although this is controversial and remains the focus of clinical trials. Finally, stage IV colon cancer patients are usually primarily treated with chemotherapy—this is the subject of a later chapter (see Chap. 36).

For patients with rectal cancer, adjuvant treatment has been recommended for both stage II and stage III disease. This treatment involves both chemotherapy and radiotherapy and usually begins preoperatively (see Chap. 28). After surgery, clinical stage II and stage III rectal cancer patients are recommend to undergo adjuvant postoperative chemotherapy regardless of the final surgical pathology. As with stage I colon cancer, surgery alone is highly successful for patients with stage I rectal cancer. This chapter will present the current recommendations regarding the use of postoperative adjuvant therapy for stage II and stage III colon and rectal cancer.

Colon Cancer

Stage III Colon Cancer

Adjuvant chemotherapy is recommended for all stage III colon cancer patients because it decreases recurrence and increases survival when compared to surgery alone [3, 4]. After surgery alone for stage III colon cancer, overall 5-year survival is 40–60 % [5]. Current chemotherapeutic regimens improve overall survival to 70–80 % [6]. Thus, 5-year overall survival of stage III colon cancer patients improves by an absolute 20–25 % with adjuvant chemotherapy. Table 33-1 summarizes the results of key clinical trials establishing the efficacy of adjuvant chemotherapy for nonmetastatic colon cancer [4, 6–11]. If all patients with stage III colon cancer receive adjuvant chemotherapy, roughly 1/3 to 1/2 of disease recurrences would be prevented.

Given the significant survival benefit of adjuvant chemotherapy, colon and rectal surgeons need to ensure that their stage III colon cancer patients are evaluated for chemotherapy after surgery. The National Quality Forum has endorsed two metrics regarding the treatment of stage III colon cancer patients [2]. The first metric estimates how many stage III patients are referred or treated with chemotherapy whereas the second metric looks at the timeliness of the administration

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Table 33-1. Key clinical trials establishing the efficacy of adjuvant chemotherapy for colon cancer

Trial	Tumor stage	Comparison	Results	Conclusion
INT 0035 1990	Stage III	Surgery alone vs. 5-FU/levamisole	3 Years survival 5-FU/levamisole 71 % Surgery alone 55 %	Postop adjuvant chemo improves survival for stage III colon cancer
IMPACT 1995	Stage III	Surgery alone vs. 5-FU/leucovorin	3 Years survival 5-FU/leucovorin 71 % Surgery alone 62 %	Postop adjuvant chemo improves survival for stage III colon cancer
QUASAR 2000	Stage III	5-FU/levamisole vs. 5-FU/folinic acid vs. 5-FU/placebo	Decreased survival and increased recurrence with levamisole compared with placebo	Postop adjuvant chemo with levamisole inferior to placebo
IMPACT 1999	Stage II	Surgery alone vs. 5-FU/leucovorin	5 Years survival = no difference 5-FU/leucovorin 82 % Surgery alone 80 %	Postop adjuvant chemo does not improve survival for stage II colon cancer
NSABP (CO-1, CO-2, CO-3, and CO-4) 1999	Stage II	Surgery alone vs. 5-FU +	5-Year survival improved with adjuvant treatment 30 % Mortality reduction with adjuvant treatment	Postop adjuvant chemo improves survival for stage II colon cancer
MOSAIC 2009	Stage II and III	FOLFOX vs. 5-FU/leucovorin	6-Year survival in stage III only FOLFOX 73 % 5-FU/Leucovorin 68 %	FOLFOX superior to 5-FU/LV for stage III colon cancer
XELOXA 2011	Stage III	XELOX vs. 5-FU/leucovorin	3 Year disease-free survival: XELOX 71 % 5-FU/Leucovorin 67 %	Capecitabine plus oxaliplatin superior to 5-FU/leucovorin

of chemotherapy. Specifically, the first metric (measure 0385) determines the percentage of patients ≥18 years old who are either referred for adjuvant chemotherapy, prescribed adjuvant chemotherapy, or have previously received adjuvant chemotherapy in the last 12 months. The other metric (measure 0223) determines the percentage of patients under the age of 80 for whom adjuvant chemotherapy is considered or administered within 4 months of the *diagnosis*. Thus, it is important for colon and rectal surgeons to promptly refer all stage III colon cancer patients for adjuvant chemotherapy.

For patients with stage III colon cancer, the National Comprehensive Cancer Network (NCCN) guidelines recommend adjuvant treatment with FOLFOX or CapeOx for 6 months [12]. FOLFOX has been found to be superior to 5-FU/leucovorin [6, 13], and CapeOx is superior to bolus 5-FU/leucovorin [14, 15]. While used frequently in patients with metastatic disease, biologic therapy with antibodies directed at VEGF-A (bevacizumab) and EGFR antibody (panitumumab, cetuximab) is not recommended for adjuvant therapy of stage III disease [16–19]. The current FOLFOX regimen, mFOLFOX6, and the CapeOx regimen are outlined in Table 33-2. These agents act in different ways on colon cancer cells. 5-Fluorouracil is a pyrimidine analog that incorporates into DNA to stop DNA synthesis. Capecitabine is an oral 5-FU prolog and thus works in the same way as 5-FU. Folinic acid (leucovorin) is a vitamin B derivative that increases the cytotoxicity of 5-FU. Oxaliplatin inhibits DNA synthesis by forming inter- and intra-strand cross-links in DNA preventing replication and transcription. Using FOLFOX, the survival benefit of adding oxaliplatin to 5-FU does come at a price, the added side effect of peripheral sensory neuropathy (PSN). While 40–50 % of patients given oxaliplatin will develop PSN, only 10–20 % of patients will have grade 3 PSN which is defined as severe symptoms limiting activities of daily living [20]. Fortunately only 1 % of patients will have grade 3 PSN at 12 months after treatment [6]. Since the benefit of the addition of oxaliplatin to 5-FU/leucovorin is unproven in patients over the age of 70, capecitabine alone or 5-FU/leucovorin should be considered in elderly patients with stage III colon cancer [12]. Capecitabine-based regimens can be particularly complicated by palmar-plantar erythrodyskinesia (hand-foot syndrome), but this side effect can be limited by symptomatic treatment and resolves after treatment is concluded [21].

Stage II Colon Cancer

The 5-year overall survival of patients with stage II colon cancer is 65–85 % with surgery alone [22]. Unlike stage III disease, the role of adjuvant chemotherapy in stage II disease remains controversial, with some studies showing a benefit [10] and others showing no benefit [23]. If there is a benefit to adjuvant chemotherapy in stage II colon cancer patients, the benefit does not improve survival by more than 5 % unlike the 25–30 % improvement for stage III patients receiving adjuvant chemotherapy [12].

Following surgery for stage II colon cancer, the current NCCN guidelines (February 2015) recommend observation (surgery alone), enrollment in a clinical trial or adjuvant chemotherapy [12]. To sort out these options, a detailed discussion with the patient is recommended to highlight the potential benefits and risks of chemotherapy. Any high-risk features should be identified and discussed (Table 33-3). Patients with or without high-risk features should consider observation,

Table 33-2. Current recommended adjuvant chemotherapy regimens for stage III colon cancer

Regimen	Agents and dosage	Frequency
mFOLFOX6	Oxaliplatin 85 mg/m^2 IV over 2 h, day 1	Every 2 weeks
	Leucovorin 400 mg/m^2 IV over 2 h, day 1	
	5-FU 400 mg/m^2 IV bolus on day 1, then 1200 mg/m^2/day × 2 days IV continuous infusion	
CapeOx	Oxaliplatin 130 mg/m^2 IV over 2 h, day 1	Every 3 weeks
	Capecitabine 850–1000 mg/m^2 PO twice daily for 14 days	

Table 33-3. High-risk factors for recurrence

- Poorly differentiated histology (exclusive of those that are MSI-H)
- Lymphatic/vascular invasion
- Perineural invasion
- Close, indeterminate, or positive margins
- Bowel obstruction
- Localized perforation
- Less than 12 lymph nodes examined

clinical trial or chemotherapy with capecitabine or 5-FU/leucovorin. Only those patients with high-risk features should be considered candidates for FOLFOX or CapeOx. It is important to remember that the addition of oxaliplatin has not been shown to improve survival in stage II colon cancer patients [6]. Finally, decision-making regarding the use of adjuvant chemotherapy for stage II disease may be aided by performing genetic testing of the tumor after surgical resection.

Genetic testing of stage II tumors has been shown to be independently predictive of prognosis. High microsatellite instability (MSI-H) or defective mismatch repair (dMMR) status has been shown to be associated with a lower recurrence rate (11 % vs. 26 %) after surgical resection alone [24]. In addition, MSI-H tumors do not benefit from 5-FU adjuvant therapy [24]. Thus, MSI/MMR testing is recommended in all patients with stage II disease in order to avoid giving adjuvant chemotherapy in patients who will derive no benefit from it. In addition to MSI/MMR testing, multigene colon cancer assays such as Oncotype Dx, ColoPrint, and ColDx are now available that can also predict prognosis and risk of recurrence. All three of these multigene assays predict recurrence independent from other factors such as TNM stage, MMR status, tumor grade, and nodes [25–31]. While these assays provide additional information regarding prognosis and recurrence risk, they are not predictive of the potential benefit of chemotherapy, and consequently are, to date, of limited clinical value.

Radiotherapy for Colon Cancer

Radiotherapy plays a limited role in patients with colon cancer. A few retrospective, single institution studies have shown that adjuvant radiotherapy improves local control for colon cancer patients at high risk of recurrence after surgery [32–34]. Unfortunately, the single randomized prospective trial comparing chemotherapy alone with combined chemotherapy and radiotherapy lacks sufficient power to draw valid conclusions [35]. Current NCCN guidelines recommend that radiotherapy for colon cancer be considered in patients with T4 tumors with penetration to a fixed structure [12]. The radiation field should include the tumor bed as defined by preoperative imaging and the placement of surgical clips at the time of operation. A dose of 45–50 Gy in 25–28 fractions is recommended and should be delivered with concomitant 5-FU chemotherapy [12]. Thus, the colorectal surgeon should always be ready to place clips in and around the tumor bed during operations involving the resection of a fixed T4 colon tumor in order to help direct postoperative radiotherapy. Neoadjuvant chemoradiotherapy can be considered for select patients with bulky tumors invading other structures.

Rectal Cancer

Treatment of patients suffering from rectal cancer is far more complex than treatment of patients with colon cancer, due to the multitude of therapeutic options and timing of those therapies. In addition, pretreatment staging is not always accurate, and this imprecision must be taken into account when planning treatment. Initial staging, neoadjuvant therapy, and surgical treatment are covered in other chapters, and thus we will focus on postoperative therapy.

Decisions regarding postoperative adjuvant treatment for rectal cancer are based primarily on tumor location, clinical stage, histologic stage, and history of neoadjuvant therapy. Proximal rectal/rectosigmoid tumors are located at least 12 cm proximal to the anal verge and are above the peritoneal reflection. Although somewhat controversial, non-advanced proximal rectal/rectosigmoid tumors are treated in the same fashion as tumors elsewhere in the colon, with surgical resection followed by postoperative chemotherapy for stage III and select stage II tumors. Tumors of the middle/lower rectum are located from 0 to 12 cm from the anal verge as measured by rigid proctoscopy [36]. They typically have a worse prognosis, stage for stage, when compared to more proximal tumors and thus treatment recommendations are slightly different.

Patients Who Did not Undergo Neoadjuvant Therapy

Like stage I colon cancer, 5-year survival after surgery alone for stage I rectal cancer exceeds 90 % [37]. Thus, no adjuvant treatment is recommended for patients undergoing proctectomy alone who are found to have T1-2N0M0 disease, assuming that margins of resection are negative for tumor. For those found to have stage II or III disease after proctectomy, decision-making

is more complex. Postoperative chemotherapy is indicated for patients with stage III disease, but the benefit for stage II disease is less certain. Postoperative radiotherapy should be considered for patients with stage II and III disease, but this recommendation is primarily based on data from the past, when there was little emphasis on surgical quality or assessment of circumferential radial margins. Postoperative radiotherapy is also associated with substantial long-term toxicity, most notable in patients undergoing restorative proctectomy. The recommendation for routine postoperative radiotherapy for patients with T3N0 disease with negative circumferential margins has thus been questioned, including in the most recent iteration of the ASCRS Practice Parameters for the Management of Rectal Cancer [38]. Even for patients with N+ disease, it is unclear whether the small benefit of postoperative radiotherapy in terms of local control is worth the risk of toxicity, which can be substantial.

If patients are to be treated with postoperative chemoradiotherapy, it is usually administered using a sandwich technique. This involves giving chemotherapy (FOLFOX or CapeOx) followed by chemoradiotherapy (Capecitabine + radiation or infusional 5FU + radiation) followed by more chemotherapy (FOLFOX or CapeOx). The radiotherapy dose is usually 45–50 Gy in 25–28 fractions using 3 or 4 fields. External iliac nodes should be included for T4 tumors involving anterior structures, and inclusion of the inguinal nodes should be considered for tumors invading the distal anal canal. In stage II and III rectal cancer patients, postoperative chemotherapy should be administered as soon as the patient has recovered from surgery as each 4 week delay in chemotherapy results in a 14 % decrease in overall survival [39].

Patients Who Underwent Neoadjuvant Radiotherapy/Chemoradiotherapy

After neoadjuvant radiotherapy/chemoradiotherapy, decisions regarding postoperative chemotherapy are more complex. Although a recent Cochrane review concluded that postoperative adjuvant chemotherapy after resection of rectal cancer was associated with improved survival regardless of stage [40], the data come from trials as old as 1975. Thus, it is difficult to draw any firm conclusions from this meta-analysis, given that some data are derived from trials in which patients were not given neoadjuvant therapy, nor was there surgical quality control or measurement of circumferential margins. Overall, there is a paucity of data on which to rely when making decisions regarding postoperative chemotherapy for patients with rectal cancer because neoadjuvant therapy regimens, surgical quality control, and pathologic processing have evolved so rapidly in the past 30 years. This evolution is ongoing, with different neoadjuvant regimens currently under investigation.

Traditionally, patients with ypT3 or ypN+ disease have been recommended to undergo postoperative chemotherapy [36]. However, a recent meta-analysis of published data found that adjuvant fluorouracil-based chemotherapy did not improve overall survival, disease-free survival, or distant recurrences, calling these recommendations into question [41]. If chemotherapy is utilized, it is also controversial as to which regimen to utilize. Two randomized clinical trials have reported a disease-free survival advantage to FOLFOX vs. fluoropyrimidine monotherapy in patients previously treated with neoadjuvant chemoradiotherapy followed by rectal surgery [42–44]. A summary of several key clinical trials regarding chemoradiotherapy for rectal cancer is shown in Table 33-4 [40, 42–44, 48–52].

Clinicians should be aware that current NCCN guidelines for clinical stage II and III rectal cancer recommend either (1) preoperative chemoradiotherapy, surgery then postoperative chemotherapy or (2) preoperative chemotherapy followed by preoperative chemoradiotherapy then surgery (see Table 33-5) [36, 45, 46]. The total duration of perioperative therapy (preoperative chemoradiotherapy and chemotherapy) should not exceed 6 months [36]. However, as noted above, these recommendations are based on incomplete and sometimes conflicting data.

Patients Undergoing Local Excision

Due to the oncologically inferior results of local excision as compared to proctectomy, even in highly select patients, many authors have recommended treatment with adjuvant chemoradiotherapy, either in the preoperative or postoperative period. The advantage of utilizing chemoradiotherapy in the postoperative period is that T stage can be known with certainty, and one can ensure healing of the wound prior to institution of radiotherapy. The advantage of utilizing neoadjuvant chemoradiotherapy is that ypT stage correlates more closely with ypN stage than T stage correlates with N stage [53] and there may be downsizing of the tumor prior to excision. The major downside of neoadjuvant therapy combined with local excision is that wound healing may be impaired, and patients may suffer substantial morbidity as a result.

For patients treated with neoadjuvant chemoradiotherapy followed by local excision, standard radiotherapy of 50.4 Gy over 28 fractions is typically given with either 5-FU or capecitabine chemotherapy. For clinical stage T2 tumors these standard neoadjuvant regimens result in complete pathologic response rates as high as 40–60 % [54, 55]. While overall 5-year survival data are insufficient, the current data suggests that there is a 90 % 5-year survival after a complete pathologic response but only a 75 % 5-year survival if there is residual disease (ypT1 or ypT2) [55]. Thus, in select stage I patients and patients with significant comorbidities that preclude an abdominal procedure, a non-standard approach using neoadjuvant treatment with or without subsequent transanal excision may be considered (see Chap. 28).

Table 33-4. Key clinical trials establishing the efficacy of chemoradiotherapy for rectal cancer

Trial	Tumor stage	Comparison	Results	Conclusion
Swedish rectal cancer trial 1993	Stage II and III	Surgery alone vs. preop short course XRT	Local recurrence: 27 % vs. 12 %	Preop XRT decreases local recurrence, improves survival (?)
			5 Years survival: 48 % vs. 58 %	
Dutch TME rectal cancer trial 2001	Stage II and III	TME alone vs. preop XRT + TME	Local recurrence: 11.4 % vs. 5.6 %	Preop XRT improves local recurrence even with TME
			Survival: no difference	Preop XRT no effect on survival
German CAO/ARO/AIO-94 2003/2004	Stage II and III	Preop chemo XRT vs. postop chemo XRT	Local recurrence: 13 % vs. 6 %	Decreased toxicity and local recurrence with preop chemo XRT
			Toxicity: 40 % vs. 27 %	Pre vs. post: no effect on survival
			Survival: no difference	
EORTC 22921 2006	Stage II and III	XRT vs. chemo XRT	Survival benefit for ypT0-2 responders	Chemo in addition to XRT can improve survival in the subgroup of responders
Cochran review: postop chemo 2012	Stage II and III	No postop chemo vs. postop chemo after neoadjuvant	Recurrence reduced 25 %	Postop chemo reduces recurrence and death rate after neoadjuvant
			Deaths reduced 17 %	
ADORE 2014	Stage II and III	FOLFOX vs. 5-FU/leucovorin after neoadjuvant	3 Year disease-free survival: 72 % vs. 62 %	Postop FOLFOX superior to 5-FU after neoadjuvant
German CAO/ARO/AIO-04 2012/2014	Stage II and III	Neoadjuvant and adjuvant FOLFOX vs. 5-FU/ leucovorin	Complete pathologic response: 17 % vs. 13 %	Preop and postop addition of oxaliplatin improves survival and pathologic response
			3 Years survival: 76 % vs. 71 %	

XRT Radiation therapy, *TME* Total mesorectal excision, *preop* Preoperative, *postop* Postoperative, *chemoxrt* Combined chemoradiation therapy

Table 33-5. Neoadjuvant and adjuvant treatment of stage II and III rectal cancer

Option I	Capecitabine + Radiotherapy OR Infusional 5-FU + Radiotherapy	→	Surgery	→	FOLFOX OR Capecitabine + Oxalplatin	
Option II	FOLFOX OR Capecitabine + Oxaliplatin	→	Capecitabine + Radiotherapy OR Infusional 5-FU + Radiotherapy	→	Surgery	

Future of Adjuvant Treatment of Colorectal Cancer

While significant progress has been made in defining optimal cytotoxic regimens in the adjuvant treatment of colorectal cancer, several questions remain regarding the optimal duration of chemotherapy treatment, the role of radiotherapy in rectal cancer, the possibility of nonsurgical interventions for rectal cancer, and the emerging role of immunotherapy.

Clinical Trials in Stage II–III Colon Cancer

Prior studies have shown no benefit from extending adjuvant therapy beyond 6 months in patients with stage III colon cancer [56]. However, a shorter duration of chemotherapy has not been adequately investigated. CALGB 80702 is currently investigating 6 cycles (3 months) vs. 12 cycles (6 months) of FOLFOX chemotherapy in patients with resected

stage III colon cancer (NCT01150045). This will be one of 6 ongoing clinical trials evaluating 3 vs. 6 months of adjuvant oxaliplatin-based chemotherapy. A meta-analysis of these studies (IDEA) will test the non-inferiority of 3 months to a 6 months strategy. In addition to the investigation of the duration of adjuvant treatment in colon cancer, efforts are ongoing to define the role of COX inhibition on disease recurrence. Analysis of the Nurses' Health Study (NHS) and Health Professional Follow-up Study (HPFS) has shown a decreased recurrence rate in patients with a diagnosis of colon cancer with regular aspirin intake [57]. The benefit appeared to be limited to patient with COX-2 overexpressing tumors [58]. These analyses were limited by their retrospective nature and require further support from prospectively conducted trials. CALGB 80702 randomizes all enrolled subjects to celecoxib vs. placebo in order to investigate the role of COX-2 inhibition in the adjuvant treatment of colon cancer. Similarly, the ASCOLT clinical trial (NCT00565708) is randomizing patients with stage II or III disease to 3 years of aspirin vs. placebo to address the role of aspirin in preventing colorectal cancer recurrence. Finally, several studies are investigating immunotherapy as an adjuvant form of treatment in colon cancer. An ongoing phase III clinical trial is evaluating the role of cytokine-induced killer cell immunotherapy for stage III colon cancer following surgery and completion of adjuvant therapy (NCT02280278).

Clinical Trials in Stage II–III Rectal Cancer (Table 33-5)

Recent phase II and retrospective trials have investigated the role of FOLFOX as a neoadjuvant treatment for rectal cancer. These series have been associated with a remarkable complete pathological response rates and were associated with a low risk of local recurrence, questioning the role of adjuvant or neoadjuvant therapy in the era of effective combination therapy [59]. To test this question, the Alliance PROSPECT clinical trial (NCT01515787) is currently randomizing patients to neoadjuvant FOLFOX chemotherapy with selective use of chemoradiotherapy (in poor responders) vs. the standard approach of neoadjuvant chemoradiotherapy. Other studies are sequencing intense chemotherapeutic regimens followed by chemoradiotherapy in order to improve on DFS and OS. The NEOFIRINOX trial (NCT01804790) is randomizing patients with rectal cancer to intensive chemotherapy with irinotecan, oxaliplatin, and 5-FU (FOLFIRINOX) followed by chemoradiotherapy, surgery, and further adjuvant chemotherapy (capecitabine or FOLFOX) vs. a control arm of chemoradiotherapy followed by surgery and adjuvant chemotherapy (capecitabine or FOLFOX).

In order to maximize systemic therapy exposure, clinical trials are evaluating the administration of the all systemic chemotherapy prior to surgical resection. For example, the RAPIDO clinical trial (NCT01558921) is randomizing rectal cancer patients to 5×5 Gy of radiotherapy followed by 6 cycles of CAPOX and then surgery vs. standard chemoradiotherapy and further adjuvant therapy (at the treating physician's discretion). Finally, several studies are investigating nonsurgical approaches to patients with rectal cancer who have a complete clinical response to chemoradiotherapy. The Cancer Institute of San Paulo is leading a randomized clinical trial (NCT02052921) that randomizes rectal cancer patients with complete clinical response following neoadjuvant chemoradiotherapy to observation vs. surgical resection with a primary end point of 3 year DFS.

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