Chapter 16
Stage II Colon Cancer: Towards an Individualized Approach

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Introduction

Like many oncologists, the sight of a stage II colon cancer patient on my schedule draws a sigh. I know the discussion will be long and the concepts confusing even to the statistically literate; and at the end of the day, I will have to leave it up to the patient to make the decision because neither guidelines nor data in the vast majority of the cases clearly point to the correct answer of whether they should or should not receive chemotherapy. The problem is that stage II colon cancer is a wastebasket of likely different cancers biologically with SEER 5-year survival rates ranging from 66 % in stage IIA cancers to 37 % for stage IIC disease [1]. In this chapter, I will present the current state of science for stage II colon cancer with the hopes of allowing the practitioner to better risk stratify patients and thereby select those who are most likely to benefit or not benefit from adjuvant chemotherapy. I will conclude with my recommendations for specific cases with the strength of that recommendation based on the science.

Search Strategy

PICO table

Pt population	Intervention	Comparators	Outcomes studied
Pts with stage 2 colon cancer	Chemo	Observation	Disease free survival, overall survival

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N. Hyman, K. Umanskiy (eds.), *Difficult Decisions in Colorectal Surgery*,
Difficult Decisions in Surgery: An Evidence-Based Approach,
DOI 10.1007/978-3-319-40223-9_16

I searched the PubMed data base using the following MeSH terms: Colonic Neoplasms/drug therapy, Colonic neoplasms/pathology, Colonic neoplasms/surgery, chemotherapy/adjuvant, gene expression, DNA mismatch repair, fluorouracil, oxaliplatin, irinotecan, meta-analysis, randomized controlled trials. References of relevant articles were searched for missed studies. I also reviewed major abstracts relevant to these topics presented at the ASCO annual meeting and ASCO GI symposium from 2012 to 2015. Finally, I cross checked my references with those in the UpToDate article entitled "Adjuvant chemotherapy for resected stage II colon cancer." [2]

Results

Non-risk Stratified Patients

Table 16.1 lists the most relevant studies which have attempted to answer the utility of chemotherapy in stage II colon cancer. While not a perfect study, only the QUASAR trial [3] comes close to being a truly randomized trial of stage II colon cancer patients with reasonable power to answer the question of a chemotherapy benefit. All the other studies are either underpowered or are pooled subset analyses of randomized trials. Most of these are very well done scientifically, including a meta-analysis done by the Cochrane group [4], but suffer from biases inherent in pooled analysis. To this mix we also add registry data which are the weakest of all the study types in the table because of uncontrolled threats to internal validity. In the QUASAR trial, 5-FU chemotherapy resulted in a statistically significant improvement in overall survival and disease free survival. The absolute magnitude of the survival benefit was 3.6 % (95 % CI: 1–6 %) meaning you would have to treat 28 patients with chemotherapy to save one life. No other study confirms this survival advantage statistically, but most suggest a magnitude of benefit which is not inconsistent with the QUASAR results either for overall survival (OS) or at least for disease free survival (DFS) [4–11]. The exception to this are 2 registry studies from the United States and British Columbia which fail to show any advantage to chemotherapy and may even suggest it is detrimental [12, 13]. The two trials utilizing more modern oxaliplatin-based chemotherapy do not appear to show a significant improvement over 5-FU alone for stage II colon cancer patients, although they are underpowered to answer this question with any certainty [6, 11].

Risk-Stratification-Clinical and Pathologic Factors

It is important to clarify terminology surrounding risk stratification, namely the distinction between a prognostic versus a predictive factor. Prognostic factors relate to the expected outcome of patients with those factors. Predictive factors are ones which determine how well a patient will respond to a particular therapy or

Table 16.1 Role of chemotherapy for stage II colon cancer

Study	Trial type	Stage II cancer Pts	Therapies	RFS (95 % CI)	OS (95 % CI)	Strength
QUASAR [3]	RCT	2,146	5-FU vs surgery alone	0.78 (0.66–0.93)	0.82 (95 % CI: 0.7–0.95)	High
NACCP [10]	RCT (subset)	468	5-Fu vs surgery alone	71 % vs. 65 % (OR crosses 1)	5 year: 78 % vs 70 % (OR crosses 1)	Moderate
INT-0035 [9]	RCT	318	5-Fu vs surgery alone	7 years: 79 % vs 71 % (p = 0.1)	7 year: 72 % vs 72 % (p = 0.83)	Moderate
Nordic [8]	Pooled RCT	812	5-FU vs surgery alone	NR	79 % vs 79 % (p = 0.81)	Moderate
IMPACT-B2 [5]	Pooled RCT	1016	5-Fu vs surgery alone	5 year: 76 % vs 73% (p = 0.061)	5 year: 82 % vs. 80 % (p = 0.057)	Moderate
Gill et al. [7]	Pooled RCT (IMPACT-B2 + 2 additional trials)	1440	5-FU versus surgery alone	5 year: 76 % vs. 72 % (p = 0.049)	5 year: 81 % vs 80 % (p = 0.1127)	Moderate
MOSAIC [6]	RCT (subset)	899	FOLFOX vs 5-FU	5 year: 83.7 % vs 79.9 % (p = 0.258)	6 year OS: 86.9 vs 86.8 (0.986)	Moderate
NSABP C-07 [11]	RCT (subset)	699	FLOX vs 5-FU	5 year: 82.1 % vs. 80.1 %	89.7 vs 89.6	Moderate
Cochrane [4]	Meta-analysis	7097	Chemo vs. surgery alone	HR 0.83 (0.77–0.92)	HR 0.96 (0.91–1.02)	Moderate
SEER-Medicare [13]	Registry	6,234[a]	Chemo vs surgery alone	NR	5 year: 70 % vs. 69.5 %	Moderate
BCCA data base [12]	Registry	1,697[a]	Chemo vs surgery alone	5 year: 87.1 % vs. 92 % (p = 0.18)	5 year: 82.9 vs 83.3 (p = 0.561)	Moderate

NR not reported

[a]Stage II with no poor prognostic feature (obstruction/perf, T4, poor/undiff histology, >12 LN, emergent surgery)

intervention. A common fallacy to which we are all susceptible is that patients with the worst prognosis are the ones most likely to benefit from aggressive treatment. It is sometimes the case but often it is not. In stage II colon cancer, the most commonly recognized prognostic factors are as follows: T4 disease, inadequate lymph node sampling (<12 lymph nodes), poorly differentiated histology (in MSI-L/S patients), perforation, obstruction, lymphovascular invasion, perineural invasion, and positive resection margins [14]. It is very important that the reader pay special attention to the high grade tumor histology and the importance of interpreting this in the context of the mismatch repair (MMR) or microsatellite instability (MSI) status of the tumor. As we will go into detail below, tumors with MMR deficiency or MSI-H phenotype are often high grade yet have an excellent prognosis.

Whether these adverse risk factors are predictive of benefit to chemotherapy is less clear. The strongest data to suggest a benefit of chemotherapy in high risk groups comes from the British Columbia Cancer Agency (BCCA) registry which found a significant survival advantage for patients with T4 tumors who received 5-FU chemotherapy (HR 0.5 95 % CI: 0.33–0.77) [12]. In contrast neither a US Intergroup meta-analysis nor a SEER registry study could discern any differential chemotherapy advantage for high versus low risk groups [7, 13]. In the MOSAIC study utilizing oxaliplatin-based therapy, there was a suggestion of a disease free survival advantage in the high risk stage II group with 5 year DFS of 82.3 % versus 74.6 % (HR 0.72; 95 % CI: 0.5–1.02) for FOLFOX versus infusional 5-FU alone [6].

Risk-Stratification-Molecular Factors

The strongest data for both a prognostic and predictive factor exists for a deficiency in the mismatch repair pathway. It is beyond the scope of this chapter to explain the nuances of MMR deficiency and testing for it; but in brief, patients with defective MMR tumors either have a germline loss of one of the MMR proteins (MLH1, MSH2, MSH6, PMS2) or epigenetic silencing of the MLH1 promoter [15]. The former is associated with Lynch syndrome and the later often in the setting of a CpG Island methylator phenotype (CIMP). Defective MMR tumors can either be tested for using a PCR panel of 5 reference microsatellite sites; if at least 2 show instability then the tumor is characterized as MSI-H. More often in the clinical setting, immunohistochemistry testing (IHC) is used to stain for the presence or absence of one of the MMR proteins. By convention in the literature, we call a tumor as defective MMR (dMMR) if they are either MSI-H or have an absence of an MMR protein by IHC.

Table 16.2 lists the major studies which have explored the prognostic and predictive value of MMR testing in stage II colon cancer. The majority of these studies clearly show that those with dMMR stage II tumors have a superior prognosis compared to those with pMMR with hazards of recurrence or death often 50 % lower [16–20]. In the study by Sargent, et al. [19] patients with dMMR tumors who received chemotherapy had a hazard of death which was nearly three times those who were on observation (HR 2.95; 95 % CI: 1.02–8.54). The reason why this may be the case is speculative, but we know patients with dMMR often have an intense

Table 16.2 Role of dMMR as prognostic and predictive marker for stage II colon cancer

Study	dMMR colon patients	Therapies	DFS (vs pMMR)	DFS w/chemo vs w/o chemo	OS (vs pMMR)	OS w/chemo vs w/o chemo
Sargent et al. [19]	102 (stage II)	5-FU vs surgery alone	0.51 (95 % CI: 0.29–0.89)[a]	HR 2.3 (95 % CI: 0.84–6.24)	0.47 (0.26-0.83)[a]	2.95 (95 % CI:1.02–8.54)
Jover et al. [27]	76 (38 stage II)	5-Fu vs surgery alone	6 year: 71 % vs 63 % (p=0.3)	6 year: 57.7 % vs 67.6 % (p=0.6)[b]	76 % vs 71 % (p=0.5)	69.2 % vs 73.5 % (p=0.8)[b]
Kim et al.(NSABP c01-c04) [28]	98 (II and III)	5-Fu vs surgery alone	HR 0.77 (95 % CI: 0.4–1.48)[a]	Interaction p=0.68[b]	HR 0.82 (95 % CI: 0.44–1.51)	Interaction p=0.62[b]
Klingbiel et al. (PETACC-3) [18]	86 (stage II)	FOLFIRI vs 5FU	HR 0.26 (95 % CI: 0.1–0.65)	HR 1.27 (0.65–2.49)	HR 0.16 (0.04–0.64)	HR 1.47 (0.65–3.36)
Hutchings et al. (QUASAR) [17]	167 (stage II)	5-Fu vs surgery alone	RR 0.44 (95 % CI: 0.29–0.67)	2 year: 2.2 % vs 5.1 % Interaction p=0.55	NR	NR
Gavin et al (NSABP C07-C08) [16]	207 (93 stage II)	FOLFOX	HR 0.48 (95 % CI: 0.3–0.7)	Interaction 0.97	HR 0.64 (95 % CI: 0.46–0.89)	Interaction p=0.848

dMMR defective DNA mismatch repair, *pMMR* proficient mismatch repair, *NR* not reported

[a]Includes only patients not treated with chemotherapy

[b]Includes stage II and III

immune response to their tumors and are in fact the only colon cancer cohort to date where immune checkpoint inhibitors appear to be effective in the metastatic setting [21]. It is suggested that chemotherapy may blunt this immune response. This hypothesis is further corroborated by recent data suggesting that if there is a chemotherapy benefit for these patients, it is only for those with germline tumors which tend not to express the hyper-mutated phenotype [22]. These findings of a detrimental impact have not been corroborated by the other studies listed in Table 16.2. However, no study has found a clearly beneficial impact of chemotherapy for this cohort, who have an otherwise excellent prognosis. It is important to note that all of these studies are severely limited by power to test for the interaction between dMMR status and chemotherapy effect.

Several studies have also looked at other molecular mutations in the BRAF and KRAS genes including interactions of these factors with dMMR status as well as those with CpG Island methylator phenotype [16, 17, 23, 24]. No clear consensus has emerged with one study suggesting a BRAF mutation is prognostic for poorer overall survival in all stage II patients [16] and another in only those with pMMR status [23]. An additional study suggested a poorer survival for KRAS mutant tumors but not BRAF [17]. In none of the studies were KRAS, BRAF, or CIMP predictive of benefit from chemotherapy and as such have not found their way into our treatment algorithms.

Risk-Stratification-Gene Expression Profiling

Genomic Health (Redwood City, CA), developed an 12 gene recurrence panel and tested an 11 gene treatment benefit panel marketed as the Oncotype DX Colon Cancer Assay [20]. The recurrence score was able to segregate patients with stage II colon cancer into low, intermediate and high risk groups with those in the lowest risk group (44 % of patients) having a 13 % 3 year risk of recurrence and those in the highest risk group (26 % of patients) having a 21 % risk of recurrence. The recurrence score remained prognostic even after controlling for other pathologic and clinical characteristics. A further validation study using CALGB 9581 patients and a more contemporaneous cohort of patients treated with oxaliplatin in the NSABP C-07 study found similar results [25, 26]. Unfortunately, in none of these studies was the recurrence score or the treatment score able to predict the patients most likely to benefit from chemotherapy. That is, the gene panel is prognostic but not predictive, meaning the proportional benefit from chemotherapy was similar regardless of recurrence score. Can such a test be useful? The answer is, yes if small differences in absolute benefit are important to your patient. For example, assuming a 20 % proportional benefit to chemotherapy (consistent with the QUASAR data) a patient with a low risk score would expect about a 2.6 % absolute benefit from chemotherapy whereas one in the high risk group a 4.2 % absolute benefit. I have found very few patients who find these types of differences helpful in their decision making but it is a discussion that I have especially in my T3N0 pMMR patients.

Recommendations Based on the Data

1. All stage II patients should be tested for dMMR either by IHC or PCR and those with dMMR should not receive chemotherapy (evidence quality high, strong recommendation)
2. Patients with T4 tumors, high grade (pMMR), <12 LN sampled, or with perforation should receive 5-FU-based chemotherapy (evidence quality moderate, moderate recommendation)
3. Patients with T4b tumors should receive oxaliplatin based chemotherapy (evidence quality weak, moderate recommendation)
4. Patients with T3N0 pMMR tumors should be offered Oncotype DX testing to aid in decision making (evidence quality moderate, weak recommendation).

A Personal View of the Data

Stage II colon cancer confronts us with the battle of the head versus the heart. Only for dMMR patients are the two well aligned where I believe the data compel us not to offer these patients chemotherapy. For pMMR T3N0 patients with no high risk features (High grade and <12 lymph nodes positive being the main ones I pay attention to in this setting) I remain at true equipoise. I am comfortable with whatever decision my patients make and see my role as trying to ensure they understand the risks and benefits so that they can make a truly informed decision. It is in the stage IIB and IIC patients I struggle most. My heart (or my gut) wants to treat all IIB patients with fluoropyrimidine- based chemotherapy and all IIC with FOLFOX. I rationalize that the IIC patients have a worse 5 year survival than IIIB patients and therefore should be treated as aggressively, but I am at a loss to point a single piece of strong evidence to support this. Nevertheless, that is my practice.

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