ADJUVANT CHEMOTHERAPY FOR COLON CANCER

- Colorectal cancer is the third most common malignant disease and the second most frequent cause of cancer related death in the US.
- Pathological stage at the time of presentation remains the most important prognostic indicator in colorectal cancer.
  - The TNM system is now the most commonly used staging system and serves for predicting the likelihood of 5 year survival for colorectal cancer.

TNM staging system for colorectal cancer		
Stage	**TNM classification**	**Five-year survival %**
I	T1-2,N0,M0	>90
IIA	T3,N0,M0	
IIB	T4,N0,M0	60-85
IIIA	T3,N1,M0	
IIIB	T4,N1,M0	25-65
IIIC	T(any),N2,M0	
IV	T(any),N(any),M1	5-7

Primary tumor (T)
TX: Primary tumor cannot be assessed
Tis: Carcinoma in situ
T1: Tumor invades submucosa
T2: Tumor invades muscularis propria
T3: Tumor penetrates muscularis propria and invades subserosa
T4: Tumor invades other organs or perforates
Nodal status (N)
NX: Regional lymph nodes cannot be assessed
N0: No metastases in regional lymph nodes
N1: Metastases in 1-3 lymph nodes
N2: Metastases in 4 or more lymph nodes
Distant metastases (M)
MX: Cannot be determined
M0: No distant metastases
M1: Distant metastases detected

- The backbone of treatment for colorectal cancer is FU, which is usually administered with leucovorin.
- It can also be given in combination with CPT-11/oxaliplatin.
- There is data to support the superiority of combined therapy in terms of disease free survival and overall survival.
- The use of chemotherapy in patients with metastatic disease has been shown to improve survival.
- In 1990, the National Institutes of Health (NIH) recommended the administration of FU-based adjuvant therapy for all medically fit patients with completely resected stage III colon cancer, based on randomized trials that demonstrated that fluorouracil (FU) -based therapy could decrease the chance of death by approximately 30%.
- Although it is agreed that patients with stage III disease benefit from adjuvant treatment, whether all patients with stage II disease should receive such treatment remains debatable.
  - This controversy was sustained by the contradictory conclusions of two large studies.
  - The National Surgical Adjuvant Breast and Bowel Project concluded that the relative benefits of treatment were largely the same for stage II and stage III tumors
  - whereas the International Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) failed to demonstrate a statistically significant benefit for stage II tumors.

- According to insurance-claims data, 27% of medicare beneficiaries with stage II colon cancer received adjuvant therapy.

Adjuvant chemotherapy use for medicare beneficiaries with stage II colon cancer (J Clin Onc Oct 02)
- Medicare reviewed 3151 pts, aged between 65-75 who underwent colon resection for stage II cancer and found that 27% of these patients received chemotherapy.
- Younger age, unfavorable tumor pathology, low comorbidities and white race were all associated with higher likelihood of receiving adjuvant therapy.
- The 5 year survival was 75% in the non-treated group and 78% in the treated group, with no statistical significance.

Pooled analysis of FU based adjuvant therapy for stage II and III colon cancer: Who benefits and how much? (J Clin Onc May 04)
- Seven randomized trials comparing 5FU/leucovorin to surgery alone: 3302 patients.
- Five-year disease free survival was 55% in the surgery alone group comparing to 67% in the adjuvant therapy group.
- Overall 5-year survival improved from 64% to 71% with treatment.
- Univariate analysis showed significant benefit for node positive disease, low grade disease and T3-4 tumors.
- Significant improvement in disease free survival for stage II patients was found, however, overall survival was unchanged with treatment.

ASCO recommendations on adjuvant chemotherapy for stage II colon cancer (J Clin Onc, Aug 04)
- **Direct evidence** from randomized controlled trials does not support the routine use of adjuvant chemotherapy for patients with stage II colon cancer.
- The decision whether to administer adjuvant therapy should be based on discussions with the patient.
- Based on the data, ASCO published their recommendations on adjuvant chemo for stage II colon cancer.
    - They defined a subgroup of stage II patients with poor prognostic factors:
        - patients with inadequately sampled lymph nodes (<13)
        - Patients with T4 tumors
        - perforated or obstructing tumors or poorly differentiated tumors.
    - However, these prognostic factors does not predict a better response to treatment.
    - They concluded that direct evidence from RCTs does not support the use of adjuvant chemotherapy, even for patients with high risk colon cancer.
- However, one may obtain indirect evidence of benefit by generalizing from the positive results of adjuvant chemo in patients with stage III disease.
- Therefore, the decision making in treatment of stage II colon cancer, should incorporate patients choice.

Systemic therapy for colorectal cancer (NEJM Feb 04)

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