Comparison of Clinical and Pathologic Outcomes and Between Patients With Stage II Colon Cancer Who Did And Did Not Receive Postoperative Adjuvant Chemotherapy

Cerrahi Tedavi Sonrası Adjuvan Kemoterapi Alan ve Almayan Evre II Kolon Kanserli Hastaların Klinik ve Patolojik Özelliklerinin Karşılaştırılması

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Abstract: The aim of this study is to compare clinical and pathologic outcomes and survival between patients with stage II colon cancer who did and did not receive postoperative adjuvant chemotherapy. A retrospective examination was made of the records of patients with stage II colon cancer who underwent surgery and followed up in our clinic. Patients were compared with regards to several clinicopathological features such as age, sex, tumor size and stage, number of nodes retrieved, the presence of lymphovascular invasion, tumor localization, signs of intestinal perforation or obstruction at presentation, disease-free and overall survival rates. A total of 57 patients with stage II colon cancer were included in the study. Overall 43 (%75, 4) patients received postoperative adjuvant chemotherapy and the remainder [n=14 (%24,6)] underwent curative surgery alone. Of the patients with a diagnosis of T4 lesion (n=26), 23 (%53, 5) received postoperative adjuvant chemotherapy. The presence of T4 lesion was found to be significantly associated with recurrence (p: 0.015) but not with overall survival (p: 0, 89). Neither the clinical nor the pathologic features of patients who received chemotherapy were significantly associated with survival or recurrence. Patients with stage II colon cancer should be treated with the treatment of individual characteristics.

Key words: stage II colon cancer, postoperative adjuvant chemotherapy.

Aydin Buyruk B, Altundag O. 2018, Comparison of Clinical and Pathologic Outcomes and Between Patients With Stage II Colon Cancer Who Did And Did Not Receive Postoperative Adjuvant Chemotherapy, *Osmangazi Tıp Dergisi*, 40 (1):64-70
Doi: 10.20515/otd.334985

Özet: Bu çalışmanın amacı, evre II kolon kanseri nedeniyle postoperatif adjuvan kemoterapi alan ve almayan hastalar arasındaki klinik ve patolojik özellikleri ve sağkalımı karşılaştırmaktır. Evre II kolon kanseri nedeniyle opere edilen ve kliniğimizde takip edilen hastaların kayıtları retrospektif olarak incelendi. Hastalar yaş, cinsiyet, tümör boyutu ve evresi, alınan lenf nodu sayısı, lenfovasküler invazyon varlığı, tümör lokalizasyonu, tanı sırasındaki bağırsak perforasyonu veya obstrüksiyon bulguları, hastalıksız ve genel sağkalım oranları gibi çeşitli klinikopatolojik özellikler bakımından karşılaştırıldı. Evre II kolon kanseri olan toplam 57 hasta çalışma kapsamına alındı. Toplam 43 (% 75,4) hastaya ameliyat sonrası adjuvan kemoterapi, kalan 14 hastaya (% 24,6) sadece küratif cerrahi uygulandı. . T4 lezyonlu (n = 26) hastaların 23'ünde (% 53,5) postoperatif adjuvan kemoterapi uygulandı. T4 lezyon varlığının rekürrens üzerine etkisi istatiksel olarak anlamlı bulundu (p = 0.015).Ancak genel sağkalıma etkisi saptanmadı (p = 0.89). Kemoterapi alan hastaların klinik veya patolojik özellikleri, sağkalım veya rekürrens ile anlamlı şekilde ilişkili bulunmamıştır. . Evre II kolon kanserli hastaların tedavi alıp almamasına bireysel özelliklerin değerlendirilmesiyle karar verilmelidir.

Anahtar Kelimeler: evre II Kolon Kanser, Postoperatif adjuvan kemoterapi

Aydın Buyruk B, Altundağ Ö. 2018, Cerrahi Tedavi Sonrası Adjuvan Kemoterapi Alan ve Almayan Evre II Kolon Kanserli Hastaların Klinik ve Patolojik Özelliklerinin Karşılaştırılması, *Osmangazi Journal of Medicine* , 40 (1):64-70
Doi: 10.20515/otd.334985

Geliş Tarihi / Received
16.08.2017

Kabul Tarihi / Accepted:
27.02.2017

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1. Introduction

Colon adenocarcinoma is the most common malignancy of the gastrointestinal tract. Over 75% of the cancer cases either are localized to the tissue or spread to the regional lymph nodes and surgery is, almost always, the sole curative treatment option. Yet, recurrence may occur even after surgical treatment (1). Patients classified as stage II (T3-4/N0) colon cancer account for almost ¼ of overall patients and have a good prognosis with surgery alone. Survival for patients with stage II colon cancer, who undergo curative surgery-alone, has been reported to be between70 to 80% (2). Some stage II patients, particularly those with node-positive disease, may, nevertheless, experience recurrence (3). While, adjuvant chemotherapy in patients with stage II colon cancer is still controversial, several meta-analyses reported % 30 improvement in survival in patients with stage II colon cancer who received adjuvant chemotherapy (4). Although the evidence is weak, adjuvant chemotherapy is recommended in high-risk patients with any of the following risk factors: T4 lesion, vascular or neuro-invasion, poorly differentiated histology, questionable surgical margin, perforation at presentation, symptoms of intestinal obstruction, and fewer than 12 lymph nodes retrieved. Current data has shown that the 5-year survival rate for stage III and high-risk stage II colon cancer patients is almost equivalent (4).Several studies, however, reported no additional survival benefit for patients receiving postoperative adjuvant chemotherapy and did not recommended its routine use in patients with stage II colon cancer (5,6).

1. Material and Methods

A retrospective examination was made of the records of with stage II colon cancer who followed up in the medical oncology department of Başkent University between 1999 and 2007. TNM system classification of the American Joint Committee on Cancer was used for classification. Patients were assigned into two groups depending on whether they received or not adjuvant chemotherapy. Patients who received chemotherapy were included only if they had been followed for at least 2 years. Patients were compared with regards to the following criteria: Age, sex, tumor size and stage, number of nodes retrieved, the presence of lymphovascular invasion, tumor localization, signs of intestinal perforation or obstruction at presentation, the presence of comorbid systemic disease, and cancer history.

Patients with T4 lesion, vascular or neuro-invasion, poorly differentiated histology, questionable surgical margin, intestinal perforation or obstruction at presentation, and fewer than 12 lymph nodes retrieved were defined as high-risk patients. The relationship between survival and the number of risk factors was also assessed. Statistical analysis was performed using the SPSS for Windows 11.5 pack software and $p < 0.05$ was considered statistically significant.

2. Results

A total of 57 patients (mean age: 64.8 years; range 30-84) with stage II colon cancer were included in the study. The follow up period varied between 16 and 108 months (mean: 36 months). Overall 43 (%75, 4) patients received postoperative adjuvant chemotherapy and the remainder [n=14 (%24,6)] underwent curative surgery alone. Of these, 9 (% 20, 9) had lymphovascular invasion, 14 intestinal obstruction (% 32,6) and 3 intestinal perforation (%7,0). Among the patients receiving adjuvant chemotherapy, 30 (%69,8) had moderately differentiated, 8 (%18,6) well differentiated and 5 (%11,6) poorly differentiated tumors. Of the patients with a diagnosis of T4 lesion (n=26), 23 (%53, 5) received postoperative adjuvant chemotherapy. The rate of patients with 13 or more lymph nodes removed in the group who received chemotherapy and who did not was % 69,8 (n=30) and % 85,7 (n=12) respectively (Table 1).

Table 1.
Comparison of demographic and clinical features of patients who did or did not receive chemotherapy.

Variables	No chemotherapy (n=14)	Chemotherapy (n=43)
Age	64,8 ± 15,9	64,4 ± 9,9
Sex		
Female	10 (%71,4)	21 (%48,8)
Male	4 (%28,6)	22 (%51,2)
Comorbid disease	8 (%57,1)	19 (%44,2)
History of cancer	-	2 (%4,7)
Pathology		
Mucinous adenocarcinoma	7 (%50,0)	11 (%25,6)
Adenocarcinoma	7 (%50,0)	32 (%74,4)
Grade		
Well differentiated	2 (%14,3)	8 (%18,6)
Moderately differentiated	11 (%78,6)	30(%69,8)
Poorly differentiated	1 (%7,1)	5 (%11,6)
Lymphovascular invasion	3 (%21,4)	9 (%20,9)
Perforation	-	3 (%7,0)
Obstruction	2 (%14,3)	14(%32,6)
T4 Lesion	3 (%21,4)	23(%53,5)
Tumor size	5 (2-17)	5 (2-12)
Number of lymph nodes >12	12 (%85,7)	30(%69,8)

During follow up 12 (%21,1) patients experienced recurrence. Of these 11 had received postoperative adjuvant chemotherapy. The presence of T4 lesion was found to be significantly associated with recurrence (p: 0.015) but not with overall survival (p: 0, 89). Similarly, the presence of lymphovascular invasion was significantly associated with recurrence (p: 0,064) but not with overall survival. (Table 2,3).

Table 2.
Potential factors associated with overall survival -1

Variables	Mortality	Mean survival (%95 CI)	Log Rank	p
Sex			0.23	0,631
Female	3/31 (%9,7)	98,9(83,7-114,1)		
Male	4/26 (%15,4)	72,2(65,9-78,4)		
Comorbid disease			1.06	0.303
No	6/30 (%20,0)	87,9 (72,3-103,6)		
Yes	1/27 (%3,7)	73,7 (66,3-81,0)		
Pathology			0.70	0.403
Mucinous adenocarcinoma	2/18 (%11,1)	83,2 (48,3-118,0)		
Adenocarcinoma	5/39 (%12,8)	75,7 (69,5-82,0)		
Grade			1.06	0.587
Well differentiated	2/10 (%20,0)	70,5 (56,5-84,6)		
Moderately differentiated	5/41 (%12,2)	95,0 (81,5-108,6)		
Poorly differentiated	0/6 (%0,0)	-		
Lymphovascular invasion			0.15	0.700
No	6/45 (%13,3)	90,7 (76,0-105,3)		
Yes	1/12 (%8,3)	76,9 (71,8-82,0)		
Perforation			0.14	0.706
No	7/54 (%13,0)	91,7 (78,8-104,7)		
Yes	0/3 (%0,0)	-		

Table 2.
Potential factors associated with overall survival -2

Variables	Mortality	Mean survival (%95 CI)	Log Rank	p
Obstruction			1.14	0.286
No	4/41 (%9,8)	96,2 (81,5-111,0)		
Yes	3/16 (%18,8)	68,9 (59,6-78,3)		
T4 lesion			0.02	0.899
No	3/31 (%9,7)	75,0 (66,2-83,8)		
Yes	4/26 (%15,4)	92,8(77,2-108,4)		
Chemotherapy			0.02	0.877
No	1/14 (%7,1)	73,7 (73,7-73,7)		
Yes	6/43 (%14,0)	93,1(79,7-106,4)		
Risk condition			0.72	0.699
No	3/17 (%17,7)	66,9 (56,7-77,0)		
1	1/14 (%7,1)	73,9 (58,0-89,9)		
>1	3/26 (%11,5)	94,6(78,0-111,2)		
Number of LN			0.12	0.731
≤7	1/9 (%11,1)	95,6(67,7-123,5)		
>7	6/48 (%12,5)	74,3 (67,6-80,9)		
Number of LN			0.08	0.777
≤12	2/15 (%13,3)	86,8(61,2-112,5)		
>12	5/42 (%11,9)	75,3 (68,5-82,1)		
Overall	7/57 (%12,3)	92,0(79,1-104,8)	-	-

CI: Confidence interval

Table 3.
Potential factors associated with recurrence (disease-free survival) -1

Variables	Recurrence rate	Recurrence-free survival(mean) (%95GA)	Log Rank	p
Sex			0.09	0.768
Female	7/31 (%22,6)	84,4 (65,5-103,3)		
Male	5/26 (%19,3)	66,4 (55,8-77,0)		
Comorbid disease			0.082	0.365
No	8/30 (%26,7)	84,0 (66,5-101,4)		
Yes	4/27 (%14,8)	65,0 (54,2-75,8)		
Pathology			0.30	0.581
Mucinous adenocarcinoma	4/18 (%22,8)	81,2 (53,3-109,1)		
Adenocarcinoma	8/39 (%20,5)	68,5 (59,1-77,8)		
Grade			0.87	0.646
Well differentiated	1/10 (%10,0)	76,8 (63,7-90,0)		
Moderately differentiated	10/41 (%24,4)	82,1 (65,7-98,5)		
Poorly differentiated	1/6 (%16,7)	66,3 (45,4-87,2)		
Lymphovascular invasion			2.37	0.124
No	8/45 (%17,8)	89,7 (75,3-104,2)		
Yes	4/12 (%33,3)	57,4 (39,2-75,6)		
Perforation			0.38	0.537
No	11/54 (%20,4)	86,8 (72,8-100,8)		
Yes	1/3 (%33,3)	37,5 (13,7-61,3)		
Overall	12/57 (%21,1)	86,5 (73-100)	-	-

Tablo 3.

Potential factors associated with recurrence (disease-free survival) -2

Variables	Recurrence rate	Recurrence-free survival(mean) (%95GA)	Log Rank	p
Obstruction			0.73	0.393
No	7/41 (%17,1)	95,3 (83,4-107,2)		
Yes	5/16 (%31,3)	59,9 (45,0-74,8)		
T4 lesion			5.88	0.015
No	2/31 (%6,5)	79,0 (72,5-85,6)		
Yes	10/26 (%38,5)	72,2 (53,0-91,3)		
Chemotherapy			1.04	0,307
No	1/14 (%7,1)	68,7 (59,3-78,1)		
Yes	11/43 (25,6)	83,4 (68,5-98,3)		
Risk condition			3.85	0.146
No	1/17 (%5,9)	71,8 (63,9-79,7)		
1	2/14 (%14,3)	73,7 (60,6-86,8)		
>1	9/26 (%34,6)	73,9 (54,1-93,7)		
Number of LN			0.28	0.599
≤7	3/9 (%33,3)	75,9 (43,6-108,3)		
>7	9/48 (%18,8)	67,7 (58,1-77,3)		
Number of LN			1.10	0.295
≤12	5/15 (%33,3)	72,7 (45,4-100,0)		
>12	7/42 (%16,7)	70,3 (61,1-79,6)		

CI: Confidence interval

Using the univariate analysis we identified that T4 lesion, lymphovascular invasion, the presence of one or more risk factors and tumor size were associated with recurrence-free survival. None of these factors, however, were significantly associated with recurrence-free survival anymore after the multivariate analysis (Table 4).

Neither the clinical nor the pathological features of patients who received chemotherapy were significantly associated with survival or recurrence. We did not analyze this association in patients who did not receive adjuvant chemotherapy due to their low number (table 5).

Table 4.

Multivariate cox regression analysis of Potential factors associated with recurrence (disease-free survival)

Variables	Relative Risk	p	%95 CI	
			Lower limit	Upper limit
Lymphovascular invasion	3,657	0,064	0,926	14,447
T4 lesion	7,974	0,078	0,792	80,240
One risk factor	0,488	0,642	0,024	10,001
>1 risk factor	0,436	0,614	0,017	10,980
Tumor size	0,792	0,161	0,572	1,097

Table 5.
Potential factors associated with disease-free survival among patients who received chemotherapy

Variables	Recurrence rate	Recurrence-free survival(mean) (%95GA)	Log Rank	p
Sex			0,08	0,774
Female	6/21 (%28,6)	81,5 (60,7- 102,3)		
Male	5/22 (%22,7)	64,6 (52,8- 76,4)		
Comorbid disease			0,31	0,576
No	7/24 (%29,2)	81,9 (62,4- 101,3)		
Yes	4/19 (%21,1)	63,3 (51,3- 75,3)		
Pathology			1,46	0,227
Mucinous adenocarcinoma	4/11 (%36,4)	68,9 (35,5- 102,2)		
Adenocarcinoma	7/32 (%21,9)	68,0 (57,8- 78,2)		
Grade			0,55	0,758
Well differentiated	1/8 (%12,5)	75,1 (58,9- 91,3)		
Moderately differentiated	9/30 (%30,0)	79,9 (62,4- 97,4)		
Poorly differentiated	1/5 (%20,0)	64,0 (39,3- 88,6)		
Lymphovascular invasion			0,96	0,326
No	8/34 (%23,5)	85,9 (69,9- 101,9)		
Yes	3/9 (%33,3)	57,8 (37,1- 78,5)		
Perforation			0,22	0,641
No	10/40 (%25,0)	83,7 (68,2- 99,2)		
Yes	1/3 (%33,3)	37,5 (13,7- 61,3)		
Obstruction			0,59	0.444
No	6/29 (%20,7)	92,2 (77,3- 107,0)		
Yes	5/14 (%35,7)	59,0 (43,6- 74,3)		
T4 Lesion			2,87	0.090
No	2/20 (%10,0)	76,6 (66,9- 86,2)		
Yes	9/23 (%39,1)	73,0 (53,3- 92,7)		
Risk condition			1,84	0.398
No	1/10 (%10,0)	69,3 (56,9- 81,7)		
1	2/11 (%18,2)	0,9 (54,7- 87,2)		
>1	8/22 (%36,4)	74,0 (53,5- 94,5)		
Number of LN			0,25	0.619
≤7	3/8 (%37,5)	73,6 (40,2- 107,1)		
>7	8/35 (%22,9)	65,8 (54,9- 76,6)		
Number of LN			1,11	0.292
≤12	5/13 (%38,5)	69,5 (41,8- 97,2)		
>12	6/30 (%20,0)	68,7 (57,8- 79,5)		
Overall	11/43 (%25,6)	83,4 (68,5- 98,3)	-	-

CI: Confidence interval

3. Discussion

Current data has shown that the 5-year survival rate for stage III and high-risk stage II colon cancer patients is almost equivalent (4). High risk factors have been described as follows: T4 lesion, vascular or neuro-invasion, poorly differentiated histology, questionable surgical margin, intestinal perforation or obstruction at presentation, and fewer than 12 lymph nodes retrieved. Adjuvant chemotherapy is currently recommended for patients with any of these risk factors.

The presence of vascular invasion is an important prognostic factor and should, therefore, be mentioned in the pathology report. In a study performed by Quah et al. on 448 patients with stage II colon cancer, lymphovascular and neuro-invasion were shown to be associated with survival (p = 0.02) (7). Five-year survival rates for patients with and without lymphovascular or neuro-invasion were % 80 and % 92, respectively (CI:%95).Consistent with the current literature, we found that, although not significant, the presence of lymphovasular invasion was associated with a two fold increase in the risk of recurrence. Survival rates for patients with and without lymphovasular or neuro-invasion in our study were % 76, 9 and % 90,7 respectively. In a study conducted by Gill et al. (8) on 3302

patients with stage II and III colon cancer who received FU based chemotherapy, the depth of tumor invasion was found to be a remarkable prognostic factor of recurrence and overall survival. In this study we did not find a significant relationship between the presence of T4 lesion and overall survival (p=0,8). T4 lesion was significantly associated with recurrence (p = 0,015). T4 lesion was not significantly associated with either recurrence or overall survival in patients with stage II colon cancer who received chemotherapy. To conclude, T4 lesion was accepted as an independent but poor prognostic factor.

The Intergroup 0035 study, which retrospectively analyzed the medical records of 318 patients with high risk stage II colon cancer, revealed that adjuvant chemotherapy improved survival (4).When these patients were compared with a group of patients who did not receive adjuvant chemotherapy, however, survival time did not significantly differ. In our study we found that patients with stage II disease who had one or more high risk factors experienced, although non-significant, higher (%34,6) rates of recurrence (p = 0.14). Of the patients who received chemotherapy, while those with one or more high risk factors had a higher rate of recurrence as compared with those who did not have any high risk factors, the influence of one or more high risk factors on recurrence and overall survival was not significant.

Adjuvant chemotherapy improves survival by around 30% in patients with stage II colon cancer (9). It is usually administered to patients with high risk disease. The study group from the National Surgical Adjuvant Breast and Bowel Project (NSABP) reviewed the treatment protocols of 1565 patients with stage II colon cancer and found % 32 decrease in mortality and %5 increase in survival (10). Consistent with this result, we found a non- significant rise in survival time in patients who received adjuvant chemotherapy as compared with those who didn't (% 93,1 vs. % 73,7 p= 0,87). We also found a higher rate of recurrence in patients who received chemotherapy (% 25,6). Recurrence-free survival rates were higher in patients who received chemotherapy than in those who did not (% 83,4 vs. % 68,7CI:%95). Of the patients with stage II colon cancer who received chemotherapy, those with T4 lesion responded better to chemotherapy as compared with those with T3 lesion (estimated mean survival: % 90,5 ; % 95 CI). The role of chemotherapy on recurrence rates and overall survival, however, was not significant.

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1. Jemal A, Siegel R, Ward E, Murray T, Smigal C, Thun MJ, et.al. Cancer statistic.CA Cancer J Clin 2007;57:43-66
2. Nauta R, Stablein DM, Holyoke ED. Survival of patients with stage B2 colon carcinoma. The Gastrointestinal Tumor Study Group experience. Arch Surg 1989; 124:180-182.
3. Engstrom PF, Benson AB 3 rd, Saltz L.Colon Cancer Clinical Practice Guidelines in Oncology. JNCCN 2003;140-153
4. De Dosso S,Sessa C, Saletti P. Adjuvant therapy for colon cancer: present and perspectives. Cancer Treat Rev. 2009; 35: 160-166.
5. Carrato A. Adjuvant treatment of colorectal cancer. Gastrointest Cancer Res. 2008; 2(4 Suppl): 42-46.
6. Figueredo A, Coombes ME, Mukherjee S. Adjuvant therapy for completely resected stage II colon cancer. Cochrane Database Syst Rev. 2008; 3
7. Quah MH, Chou JF, Gönen M, Jinru Shia. Identification of Patients with High Risk Stage II Colon Cancer for Adjuvant Therapy. Dis Colon Rectum 2008; 51: 503-507.
8. Gill S, Loprinzi CL, Sargent DJ, et al. Pooled analysis of fluoroyracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? J Clin Oncol 2004; 22:1773-1775.
9. Benson AB, Schrag D, Somerfield MR, et al. American Society of Clinical Oncology reccommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol 2004; 22: 3408-3419
10. Mamounas E, Wieand S, Wolmark N, et al. Comparative efficacy of adjuvant chemotherapy in patients with Dukes' B versus Dukes' C colon cancer: results from four National Surgical Adjuvant Breast and Bowel Project adjuvant studies. J Clin Oncol 1999; 17: 1349-1355
11. Blum WF, Englaro P, Hanitsch S, Juul A, Hertel NT, Müller J. Plasma leptin levels in healty children and adolescent: dependence on body mass index, body fat mass, gender, pubertal stage and testosterone. J.Clin Endocrinol Metab 1997;82:2904-10