

RECOMENDACIÓN T.3

BÚSQUEDA Y SÍNTESIS DE EVIDENCIA DE EFECTOS DESEABLES E INDESEABLES

Guía de Práctica Clínica Cáncer Colorectal en Personas de 15 años y más - 2018

A. PREGUNTA CLÍNICA

En personas con diagnóstico de cáncer de colon en etapa II operado y factores de riesgo de recurrencia* ¿Se debe realizar quimioterapia adyuvante en comparación a no realizarla?

*Factores de riesgo de recurrencia: Etapa T4, obstructivo o perforado, bajo recuento ganglionar, permeaciones vasculares, brotes tumorales, infiltración perineural.

Análisis y definición de los componentes de la pregunta en formato PICO

Población: Personas con diagnóstico de cáncer de colon en etapa II operado y factores de riesgo de recurrencia (T4, obstructivo o perforado, bajo recuento ganglionar, permeaciones vasculares, brotes tumorales, infiltración perineural).

Intervención: Quimioterapia adyuvante.

Comparación: No realizar quimioterapia adyuvante.

Desenlace (outcome): Mortalidad, recurrencia, efectos adversos.

B. BÚSQUEDA DE EVIDENCIA

Se realizó una búsqueda general de revisiones sistemáticas asociadas al tema de “Colorectal cancer”. Las bases de datos utilizadas fueron: Cochrane database of systematic reviews (CDSR); Database of Abstracts of Reviews of Effectiveness (DARE); HTA Database; PubMed; LILACS; CINAHL; PsycINFO; EMBASE; EPPI-Centre Evidence Library; 3ie Systematic Reviews and Policy Briefs Campbell Library; Clinical Evidence; SUPPORT Summaries; WHO institutional Repository for information Sharing; NICE public health guidelines and systematic reviews; ACP Journal Club; Evidencias en Pediatría; y The JBI Database of Systematic Reviews and implementation Reports. No se aplicaron restricciones en base al idioma o estado de publicación. Dos revisores de manera independiente realizaron la selección de los títulos y los resúmenes, la evaluación del texto completo y la extracción de datos. Un investigador experimentado resolvió cualquier discrepancia entre los distintos revisores. En caso de considerarse necesario, se integraron estudios primarios.¹

Seleccionadas las revisiones sistemáticas o estudios primarios asociadas a la temática, se clasificaron en función de las potenciales preguntas a las que daban respuesta. Al momento de definir la pregunta la evidencia ya se encontraba previamente clasificada según intervenciones comparadas.

¹ Para revisar la metodología, las estrategias y los resultados de la búsqueda, favor revisar el informe “Búsqueda sistemática de evidencia de los efectos deseables e indeseables” en la sección de método de la Guía de Práctica Clínica respectiva.

Los resultados se encuentran alojados en la plataforma Living Overview of the Evidence (L-OVE), sistema que permite la actualización periódica de la evidencia.

C. SÍNTESIS DE EVIDENCIA

Resumen de la evidencia identificada

Se identificaron 5 revisiones sistemáticas que incluyen 97 estudios primarios, de los cuales todos corresponden a ensayos aleatorizados. Para más detalle ver “*Matriz de evidencia*”², en el siguiente enlace: [Quimioterapia adyuvante para el cáncer de colon localizado](#).

Tabla 1: Resumen de la evidencia seleccionada

Revisión Sistemática	5 [1-5]
Estudios primarios	97 [6-102]

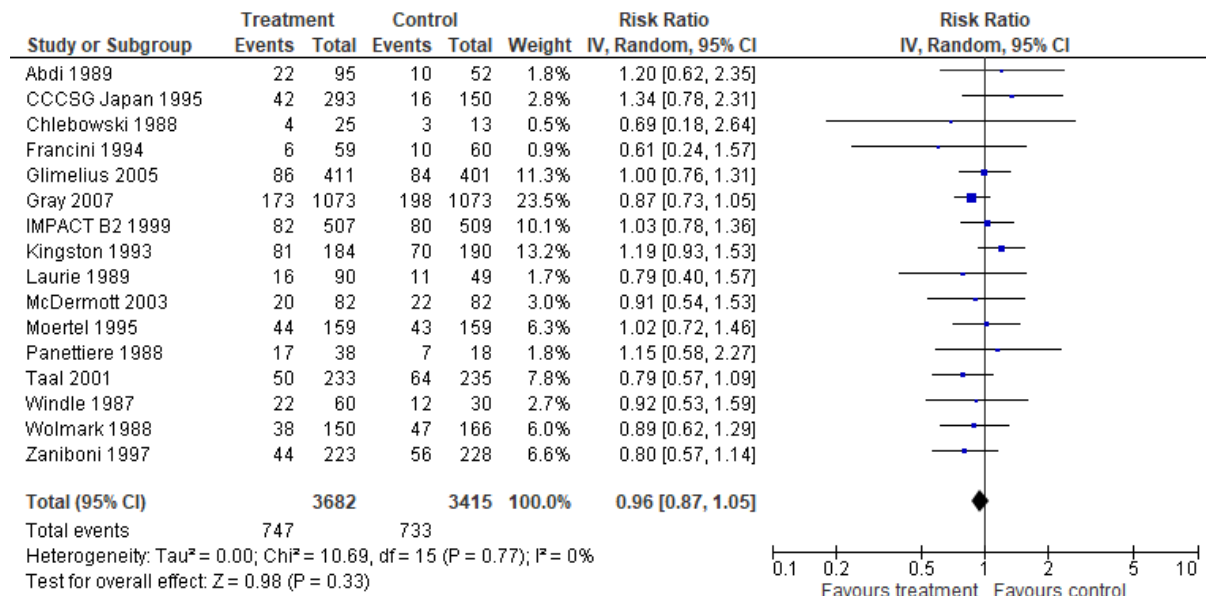
Estimador del efecto

Se realizó un análisis de la matriz de evidencia, identificando una revisión sistemática Cochrane [1] que incluye la mayoría de los ensayos aleatorizados. Al analizar los ensayos que aparecen en la matriz y no están incluidos en la revisión, se llegó a la conclusión que fueron excluidos explícitamente por razones justificadas, o fueron incluidos indirectamente, ya que la revisión Cochrane incluyó datos reportados por algunos grupos colaborativos que reportan análisis agregados de sus estudios (*pooled analysis*). Considerando lo anterior, se decidió reutilizar los datos de la revisión Cochrane para construir la tabla de resumen de resultados.

² **Matriz de Evidencia**, tabla dinámica que grafica el conjunto de evidencia existente para una pregunta (en este caso, la pregunta del presente informe). Las filas representan las revisiones sistemáticas y las columnas los estudios primarios que estas revisiones han identificado. Los recuadros en verde corresponden a los estudios incluidos en cada revisión. La matriz se actualiza periódicamente, incorporando nuevas revisiones sistemáticas pertinentes y los respectivos estudios primarios.

Metanálisis

Mortalidad



Recurrencia

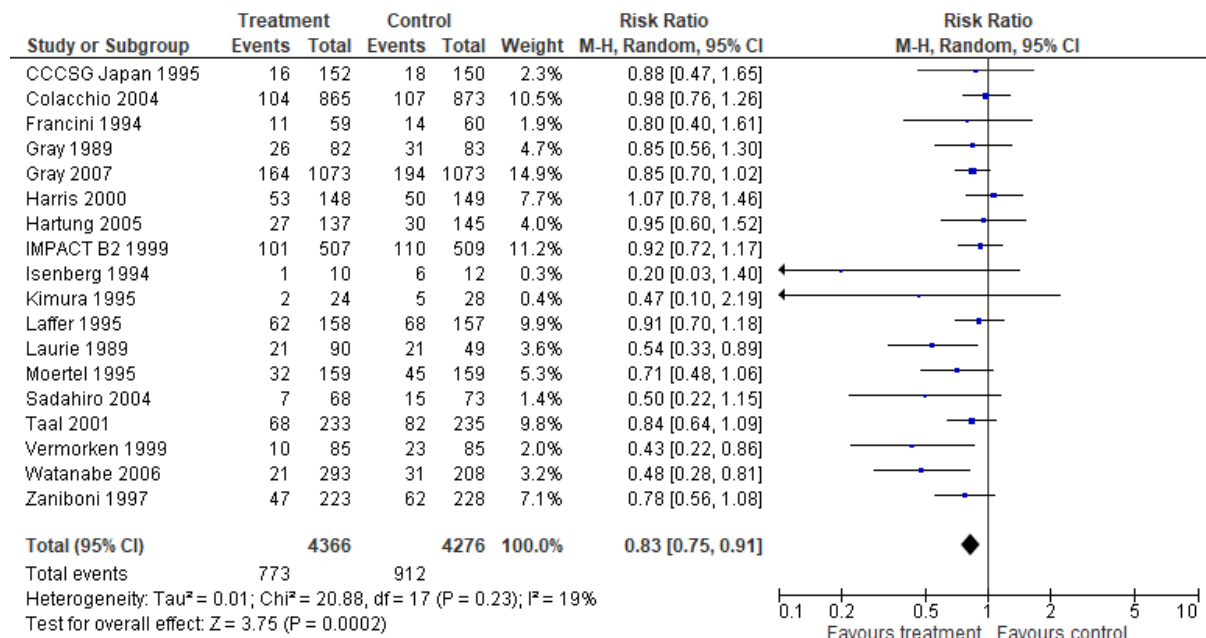


Tabla de Resumen de Resultados (Summary of Findings)

QUIMIOTERAPIA ADYUVANTE PARA CÁNCER DE COLON ETAPA II OPERADO Y CON FACTORES DE RIESGO DE RECURRENCIA.						
Pacientes	Personas con diagnóstico de cáncer de colon en etapa II operado y factores de riesgo de recurrencia (Etapa T4, obstructivo o perforado, bajo recuento ganglionar, permeaciones vasculares, brotes tumorales, infiltración perineural).					
Intervención	Realizar quimioterapia adyuvante					
Comparación	No realizarla.					
Desenlaces	Efecto relativo (IC 95%) -- Pacientes / estudios	Efecto absoluto estimado*			Certeza de la evidencia (GRADE)	Mensajes clave en términos sencillos
		SIN Quimioterapia adyuvante	CON Quimioterapia adyuvante	Diferencia (IC 95%)		
Mortalidad	RR 0,96 (0,87 a 1,05) -- 7097 pacientes / 16 ensayos en una revisión sistemática [1]	215 por 1000	206 por 1000	Diferencia: 9 menos (28 menos a 11 más)	⊕⊕⊕○ ¹ Moderada	Quimioterapia adyuvante probablemente disminuye la mortalidad en cáncer de colon etapa II operado con factores de riesgo de recurrencia.
Recurrencia	RR 0,83 (0,75 a 0,91) -- 8642 pacientes / 18 ensayos en una revisión sistemática [1]	213 por 1000	177 por 1000	Diferencia: 36 menos (19 a 53 menos)	⊕⊕⊕⊕ Alta	Quimioterapia adyuvante disminuye las recurrencias en cáncer de colon etapa II operado con factores de riesgo de recurrencia.
Efectos adversos	Ninguna de las revisiones identificadas entrega una medida de efecto, sin embargo en general concluyen que existe un aumento de los efectos adversos con terapia adyuvante.				--	--

IC 95%: Intervalo de confianza del 95%.
RR: Riesgo relativo.
GRADE: Grados de evidencia Grading of Recommendations Assessment, Development and Evaluation.
* El **riesgo SIN Quimioterapia adyuvante** está basado en el riesgo del grupo control en los estudios. El **riesgo CON quimioterapia adyuvante**(y su intervalo de confianza) está calculado a partir del efecto relativo (y su intervalo de confianza).
¹ Se disminuyó un nivel de certeza de evidencia por imprecisión, ya que cada extremo del intervalo de confianza conlleva una decisión diferente.
Fecha de elaboración de la tabla: Octubre, 2018.

Referencias

1. Dubé S, Heyen F, Jenicek M. Adjuvant chemotherapy in colorectal carcinoma: results of a meta-analysis. *Diseases of the colon and rectum*. 1997;40(1):35-41.
2. Figueredo A, Charette ML, Maroun J, Brouwers MC, Zuraw L. Adjuvant therapy for stage II colon cancer: a systematic review from the Cancer Care Ontario Program in evidence-based care's gastrointestinal cancer disease site group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2004;22(16):3395-407.
3. Figueredo A, Coombes ME, Mukherjee S. Adjuvant Therapy for completely resected Stage II Colon Cancer. *Cochrane database of systematic reviews (Online)*. 2008;(3):CD005390.
4. Sargent DJ, Wieand HS, Haller DG, Gray R, Benedetti JK, Buyse M, Labianca R, Seitz JF, O'Callaghan CJ, Francini G, Grothey A, O'Connell M, Catalano PJ, Blanke CD, Kerr D, Green E, Wolmark N, Andre T, Goldberg RM, De Gramont A. Disease-free survival versus overall survival as a primary end point for adjuvant colon cancer studies: individual patient data from 20,898 patients on 18 randomized trials. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2005;23(34):8664-70.
5. Wu X, Zhang J, He X, Wang C, Lian L, Liu H, Wang J, Lan P. Postoperative adjuvant chemotherapy for stage II colorectal cancer: a systematic review of 12 randomized controlled trials. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract*. 2012;16(3):646-55.
6. Abdi EA, Hanson J, Harbora DE, Young DG, McPherson TA. Adjuvant chemoimmuno- and immunotherapy in Dukes' stage B2 and C colorectal carcinoma: a 7-year follow-up analysis. *Journal of surgical oncology*. 1989;40(3):205-13.
7. Arnaud JP, Buyse M, Nordlinger B, Martin F, Pector JC, Zeitoun P, Adloff A, Duez N. Adjuvant therapy of poor prognosis colon cancer with levamisole: results of an EORTC double-blind randomized clinical trial. *The British journal of surgery*. 1989;76(3):284-9.
8. Bancewicz J, Calman KC, Macpherson SG, McArdle CS, McVie JG, Soukop M. Adjuvant chemotherapy and immunotherapy for colorectal cancer: preliminary communication. *Journal of the Royal Society of Medicine*. 1980;73(3):197-9.
9. Beart RW, Moertel CG, Wieand HS, Leigh JE, Windschitl HE, van Heerden JA, Fitzgibbons RJ, Wolff BG. Adjuvant therapy for resectable colorectal carcinoma with fluorouracil administered by portal vein infusion. A study of the Mayo Clinic and the North Central Cancer Treatment Group. *Archives of surgery (Chicago, Ill. : 1960)*. 1990;125(7):897-901.
10. Benson AB, Schrag D, Somerfield MR, Cohen AM, Figueredo AT, Flynn PJ, Krzyzanowska MK, Maroun J, McAllister P, Van Cutsem E, Brouwers M, Charette M, Haller DG. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2004;22(16):3408-19.
11. CCCSG Japan 1995. Five-year results of a randomized controlled trial of adjuvant chemotherapy for curatively resected colorectal carcinoma. The Colorectal Cancer Chemotherapy Study Group of Japan. *Japanese journal of clinical oncology*. 1995;25(3):91-103.
12. Chlebowski RT, Nystrom S, Reynolds R, Weiner JM, Bateman JR. Long-term survival following levamisole or placebo adjuvant treatment of colorectal cancer: a Western Cancer Study Group Trial. *Oncology*. 1988;45(3):141-3.
13. Colacchio T, Niedzwiecki D, Compton C, Warren R, Benson AIB, Goldberg R, Kerr D, Fields A, Hollis D, Mayer R.. Phase III trial of adjuvant immunotherapy with MOAb 17-1A following resection for stage II adenocarcinoma of the colon (CALGB 9581). *Annual Meeting Proceedings of the American Society of Clinical Oncology*. 2004;:251.
14. Dignam JJ, Colangelo L, Tian W, Jones J, Smith R, Wickerham DL, Wolmark N. Outcomes among African-Americans and Caucasians in colon cancer adjuvant therapy trials: findings from the National Surgical Adjuvant Breast and Bowel Project. *Journal of the National Cancer Institute*. 1999;91(22):1933-40.
15. Dixon WJ, Longmire WP, Holden WD. Use of triethylenethiophosphoramide as an adjuvant to the surgical treatment of gastric and colorectal carcinoma: ten-year follow-up. *Annals of surgery*. 1971;173(1):26-39.
16. Dwight RW, Higgins GA, Keehn RJ. Factors influencing survival after resection in cancer of the colon and rectum. *American journal of surgery*. 1969;117(4):512-22.
17. Dwight RW, Humphrey EW, Higgins GA, Keehn RJ. FUDR as an adjuvant to surgery in cancer of the large bowel. *Journal of surgical oncology*. 1973;5(3):243-9.
18. DWIGHT RW. ADJUVANT CHEMOTHERAPY IN CANCER OF THE LARGE BOWEL. AN INTERIM REPORT OF THE VETERANS ADMINISTRATION SURGICAL ADJUVANT CANCER CHEMOTHERAPY STUDY. *American journal of surgery*. 1964;107:609-13.

19. FFC2 8802. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. *Lancet*. 1995;345(8955):939-44.
20. Fielding LP, Hittinger R, Grace RH, Fry JS. Randomised controlled trial of adjuvant chemotherapy by portal-vein perfusion after curative resection for colorectal adenocarcinoma. *Lancet*. 1992;340(8818):502-6.
21. Fisher B, Wolmark N, Rockette H, Redmond C, Deutsch M, Wickerham DL, Fisher ER, Caplan R, Jones J, Lerner H. Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01. *Journal of the National Cancer Institute*. 1988;80(1):21-9.
22. Focan C, Bury J, Beauvain M, Herman ML, Vindevoghel A, Brohée D, Lecomte M. Adjuvant intraportal chemotherapy for Dukes B2 and C colorectal cancer also receiving systemic treatment: results of a multicenter randomized trial. Groupe Régional d'Etude du Cancer Colo-Rectal (Belgium). *Anti-cancer drugs*. 2000;11(7):549-54.
23. Francini G, Petrioli R, Lorenzini L, Mancini S, Armenio S, Tanzini G, Marsili S, Aquino A, Marzocca G, Civitelli S. Folinic acid and 5-fluorouracil as adjuvant chemotherapy in colon cancer. *Gastroenterology*. 1994;106(4):899-906.
24. Gastrointestinal Tumor Study Group. Adjuvant therapy of colon cancer--results of a prospectively randomized trial. *The New England journal of medicine*. 1984;310(12):737-43.
25. Gastrointestinal Tumor Study Group. Survival after postoperative combination treatment of rectal cancer. *N Engl J Med*. 1985;312:1465-72.
26. GERCOR C96.1. André T, Quinaux E, Louvet C, Colin P, Gamelin E, Bouche O, Achille E, Piedbois P, Tubiana-Mathieu N, Boutan-Laroze A, Flesch M, Lledo G, Raoul Y, Debrix I, Buyse M, de Gramont A. Phase III study comparing a semimonthly with a monthly regimen of fluorouracil and leucovorin as adjuvant treatment for stage II and III colon cancer patients: final results of GERCOR C96.1. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2007;25(24):3732-8.
27. Gilbert JM, Hellmann K, Evans M, Cassell PG, Taylor RH, Stoodley B, Ellis H, Wastell C. Randomized trial of oral adjuvant razoxane (ICRF 159) in resectable colorectal cancer: five-year follow-up. *The British journal of surgery*. 1986;73(6):446-50.
28. Gill S, Loprinzi CL, Sargent DJ, Thomé SD, Alberts SR, Haller DG, Benedetti J, Francini G, Shepherd LE, Francois Seitz J, Labianca R, Chen W, Cha SS, Heldebrant MP, Goldberg RM. Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much?. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2004;22(10):1797-806.
29. GIVIO protocol SITAC-01. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. *Lancet*. 1995;345(8955):939-44.
30. Glimelius B, Dahl O, Cedermark B, Jakobsen A, Bentzen SM, Starkhammar H, Grönberg H, Hultborn R, Albertsson M, Pählman L, Tveit KM, Nordic Gastrointestinal Tumour Adjuvant Therapy Group. Adjuvant chemotherapy in colorectal cancer: a joint analysis of randomised trials by the Nordic Gastrointestinal Tumour Adjuvant Therapy Group. *Acta oncologica (Stockholm, Sweden)*. 2005;44(8):904-12.
31. Graf W, Westlin JE, Pählman L, Glimelius B. Adjuvant intraperitoneal 5-fluorouracil and intravenous leucovorin after colorectal cancer surgery: a randomized phase II placebo-controlled study. *International journal of colorectal disease*. 1994;9(1):35-9.
32. Grage TB, Moss SE. Adjuvant chemotherapy in cancer of the colon and rectum: demonstration of effectiveness of prolonged 5-FU chemotherapy in a prospectively controlled, randomized trial. *The Surgical clinics of North America*. 1981;61(6):1321-9.
33. Gray BN, Walker C, Andrewartha L, Freeman S, Bennett RC. Controlled clinical trial of adjuvant immunotherapy with BCG and neuraminidase-treated autologous tumour cells in large bowel cancer. *Journal of surgical oncology*. 1989;40(1):34-7.
34. Gray R, James R, Mossman J, Stenning S. AXIS--a suitable case for treatment. UK Coordinating Committee on Cancer Research (UKCCCR) Colorectal Cancer Subcommittee. *British journal of cancer*. 1991;63(6):841-5.
35. Grossi CE, Wolff WI, Nealon TF, Pasternack B, Ginzburg L, Rousselot LM. Intraluminal fluorouracil chemotherapy adjunct to surgical procedures for respectable carcinoma of the colon and rectum. *Surgery, gynecology & obstetrics*. 1977;145(4):549-54.
36. Hafström L, Rudenstam CM, Domellöf L. A randomized trial of oral 5-fluorouracil versus placebo as adjuvant therapy in colorectal cancer Dukes' B and C: results after 5 years observation time. *The British journal of surgery*. 1985;72(2):138-41.

37. Hanna MG, Hoover HC, Vermorken JB, Harris JE, Pinedo HM. Adjuvant active specific immunotherapy of stage II and stage III colon cancer with an autologous tumor cell vaccine: first randomized phase III trials show promise. *Vaccine*. 2001;19(17-19):2576-82.
38. Harris JE, Ryan L, Hoover HC, Stuart RK, Oken MM, Benson AB, Mansour E, Haller DG, Manola J, Hanna MG. Adjuvant active specific immunotherapy for stage II and III colon cancer with an autologous tumor cell vaccine: Eastern Cooperative Oncology Group Study E5283. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2000;18(1):148-57.
39. Hartung G, Hofheinz RD, Dencausse Y, Sturm J, Kopp-Schneider A, Dietrich G, Fackler-Schwalbe I, Bornbusch D, Gonnermann M, Wojatschek C, Lindemann W, Eschenburg H, Jost K, Edler L, Hochhaus A, Queisser W. Adjuvant therapy with edrecolomab versus observation in stage II colon cancer: a multicenter randomized phase III study. *Onkologie*. 2005;28(6-7):347-50.
40. Higgings GA Jr, Lee LE Jr, Dwight RW, Keehn RJ.. The case for adjuvant 5-fluorouracil in colorectal cancer. *Cancer Clin Trials*. 1978;1:35-41.
41. Higgins GA, Amadeo JH, McElhinney J, McCaughan JJ, Keehn RJ. Efficacy of prolonged intermittent therapy with combined 5-fluorouracil and methyl-CCNU following resection for carcinoma of the large bowel. A Veterans Administration Surgical Oncology Group report. *Cancer*. 1984;53(1):1-8.
42. Higgins GA, Donaldson RC, Rogers LS, Juler GL, Keehn RJ. Efficacy of MER immunotherapy when added to a regimen of 5-fluorouracil and methyl-CCNU following resection for carcinoma of the large bowel. A Veterans Administration Surgical Oncology Group report. *Cancer*. 1984;54(2):193-8.
43. Higgins GA, Dwight RW, Smith JV, Keehn RJ. Fluorouracil as an adjuvant to surgery in carcinoma of the colon. *Archives of surgery (Chicago, Ill. : 1960)*. 1971;102(4):339-43.
44. Higgins GA, Humphrey E, Juler G, LeVeen HH, McCaughan J, Keehn RJ. Adjuvant chemotherapy in the surgical treatment of large bowel cancer. *Cancer*. 1976;38(4):1461-7.
45. IMPACT B2 1999. Efficacy of adjuvant fluorouracil and folinic acid in B2 colon cancer. International Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) Investigators. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1999;17(5):1356-63.
46. Intergroup 0035. Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Goodman PJ, Ungerleider JS, Emerson WA, Tormey DC, Glick JH. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *The New England journal of medicine*. 1990;322(6):352-8.
47. Intergroup 0089. Haller DG, Catalano PJ, Macdonald JS, O'Rourke MA, Frontiera MS, Jackson DV, Mayer RJ. Phase III study of fluorouracil, leucovorin, and levamisole in high-risk stage II and III colon cancer: final report of Intergroup 0089. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2005;23(34):8671-8.
48. Irvin T, Vowles KD, Golby MG. Fluorouracil in chemoprophylaxis of colorectal cancer. Results of a controlled clinical trial. *Diseases of the colon and rectum*. 1986;29(11):704-6.
49. Isenberg J, Ko H, Pulverer G, Grundmann R, Stützer H, Pichlmaier H. Preoperative immunostimulation by *Propionibacterium granulosum* KP-45 in colorectal cancer. *Anticancer research*. 1994;14(3B):1399-404.
50. Ito, Katsuki, Yamaguchi, Akihiro, Miura, Kaoru, Kato, Tomoyuki, Baba, Shozo, Matsumoto, Sumio, Ishii, Masataka, Takagi, Hiroshi. Oral adjuvant chemotherapy with Carmofur (HCFU) for colorectal cancer: Five-year follow-up. Tokai HCFU Study Group—third study on colorectal cancer. *Journal of Surgical Oncology*. 1996;63(2):107-111.
51. Kato T, Ohashi Y, Nakazato H, Koike A, Saji S, Suzuki H, Takagi H, Nimura Y, Hasumi A, Baba S, Manabe T, Maruta M, Miura K, Yamaguchi A. Efficacy of oral UFT as adjuvant chemotherapy to curative resection of colorectal cancer: multicenter prospective randomized trial. *Langenbeck's archives of surgery / Deutsche Gesellschaft für Chirurgie*. 2002;386(8):575-81.
52. Kimura O, Kurayoshi K, Hoshino K, Sugezawa A, Makino M, Kaibara N. Prophylactic portal infusion chemotherapy as adjuvant therapy for the prevention of metachronous liver metastasis in colorectal cancer. *Surgery today*. 1995;25(3):211-6.
53. Kingston RD, Fielding JW, Palmer MK. An evaluation of the effectiveness and safety of razoxane when used as an adjunct to surgery in colo-rectal cancer. Report of a controlled randomised study of 603 patients. *International journal of colorectal disease*. 1993;8(2):106-10.
54. Krook JE, Moertel CG, Gunderson LL, Wieand HS, Collins RT, Beart RW, Kubista TP, Poon MA, Meyers WC, Mailliard JA. Effective surgical adjuvant therapy for high-risk rectal carcinoma. *The New England journal of medicine*. 1991;324(11):709-15.

55. Laffer U, Metzger U, Aeberhard P, Maibach R, Castiglione M, Goldhirsch A, et al.. Long-term results of single course of adjuvant intraportal chemotherapy for colorectal cancer. Swiss Group for Clinical Cancer Research (SAKK). *Lancet*. 1995;345(8946):349-53.
56. Lawrence W, Terz JJ, Horsley JS, Brown PW, Romero C. Chemotherapy as an adjuvant to surgery for colorectal cancer. A follow-up report. *Archives of surgery (Chicago, Ill. : 1960)*. 1978;113(2):164-8.
57. Mamounas E, Wieand S, Wolmark N, Bear HD, Atkins JN, Song K, Jones J, Rockette H. 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 (C-01, C-02, C-03, and C-04). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1999;17(5):1349-55.
58. McCollum AD, Catalano PJ, Haller DG, Mayer RJ, Macdonald JS, Benson AB, Fuchs CS. Outcomes and toxicity in african-american and caucasian patients in a randomized adjuvant chemotherapy trial for colon cancer. *Journal of the National Cancer Institute*. 2002;94(15):1160-7.
59. McDermott U, Boyd RE, Houston RF, Kee F, McAleer JJ, Millar J, McAdams T, Sloan JM, Moorehead RJ, Wison RH.. A phase III trial of short duration adjuvant chemotherapy with bolus/infusional 5 fluorouracil (FU) and folinic acid (FA) versus surgery alone in dukes' B and C colorectal cancer (CRC). *Proceedings of the American Society of Clinical Oncology*. 2003;
60. Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Tangen CM, Ungerleider JS, Emerson WA, Tormey DC, Glick JH. Intergroup study of fluorouracil plus levamisole as adjuvant therapy for stage II/Dukes' B2 colon cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1995;13(12):2936-43.
61. MRAZEK R, ECONOMOU S, MCDONALD GO, SLAUGHTER DP, COLE WH. Prophylactic and adjuvant use of nitrogen mustard in the surgical treatment of cancer. *Annals of surgery*. 1959;150:745-55.
62. NCCTG 784852. Laurie JA, Moertel CG, Fleming TR, Wieand HS, Leigh JE, Rubin J, McCormack GW, Gerstner JB, Krook JE, Malliard J. Surgical adjuvant therapy of large-bowel carcinoma: an evaluation of levamisole and the combination of levamisole and fluorouracil. The North Central Cancer Treatment Group and the Mayo Clinic. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1989;7(10):1447-56.
63. NCCTG 874651. O'Connell MJ, Mailliard JA, Kahn MJ, Macdonald JS, Haller DG, Mayer RJ, Wieand HS. Controlled trial of fluorouracil and low-dose leucovorin given for 6 months as postoperative adjuvant therapy for colon cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1997;15(1):246-50.
64. NCCTG 894651. O'Connell MJ, Laurie JA, Kahn M, Fitzgibbons RJ, Erlichman C, Shepherd L, Moertel CG, Kocha WI, Pazdur R, Wieand HS, Rubin J, Vukov AM, Donohue JH, Krook JE, Figueredo A. Prospectively randomized trial of postoperative adjuvant chemotherapy in patients with high-risk colon cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1998;16(1):295-300.
65. NCCTG 914653. O'Connell M, Skillings J, Windschitl H. Phase III trial of high dose levamisole (LEV) 5-fluorouracil (5FU) leucovorin (CF) as adjuvant treatment (Adj) for high risk colon cancer (CC): An NCCTG/NCIC study. *Proc Am Soc Clin Oncol*. 2001;20(132a):abstr 525.
66. NCICCTG C-03. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. *Lancet*. 1995;345(8955):939-44.
67. Nitti D, Wils J, Sahnoud T, Curran D, Couvreur ML, Lise M, Rauschecker H, dos Santos JG, Stremmel W, Roelofsen F. Final results of a phase III clinical trial on adjuvant intraportal infusion with heparin and 5-fluorouracil (5-FU) in resectable colon cancer (EORTC GITCCG 1983-1987). European Organization for Research and Treatment of Cancer. Gastrointestinal Tract Cancer Cooperative Group. *European journal of cancer (Oxford, England : 1990)*. 1997;33(8):1209-15.
68. NSABP C01. Wolmark N, Fisher B, Rockette H, Redmond C, Wickerham DL, Fisher ER, Jones J, Glass A, Lerner H, Lawrence W. Postoperative adjuvant chemotherapy or BCG for colon cancer: results from NSABP protocol C-01. *Journal of the National Cancer Institute*. 1988;80(1):30-6.
69. NSABP C02. Wolmark N, Rockette H, Wickerham DL, Fisher B, Redmond C, Fisher ER, Potvin M, Davies RJ, Jones J, Robidoux A. Adjuvant therapy of Dukes' A, B, and C adenocarcinoma of the colon with portal-vein fluorouracil hepatic infusion: preliminary results of National Surgical Adjuvant Breast and Bowel Project Protocol C-02. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1990;8(9):1466-75.
70. NSABP C03. Wolmark N, Rockette H, Fisher B, Wickerham DL, Redmond C, Fisher ER, Jones J, Mamounas EP, Ore L, Petrelli NJ. The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel Project protocol C-03. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1993;11(10):1879-87.

71. NSABP C04. Wolmark N, Rockette H, Mamounas E, Jones J, Wieand S, Wickerham DL, Bear HD, Atkins JN, Dimitrov NV, Glass AG, Fisher ER, Fisher B. Clinical trial to assess the relative efficacy of fluorouracil and leucovorin, fluorouracil and levamisole, and fluorouracil, leucovorin, and levamisole in patients with Dukes' B and C carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project C-04. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1999;17(11):3553-9.
72. NSABP C05. Wolmark N, Bryant J, Smith R, Grem J, Allegra C, Hyams D, Atkins J, Dimitrov N, Oishi R, Prager D, Fehrenbacher L, Romond E, Colangelo L, Fisher B. Adjuvant 5-fluorouracil and leucovorin with or without interferon alfa-2a in colon carcinoma: National Surgical Adjuvant Breast and Bowel Project protocol C-05. *Journal of the National Cancer Institute*. 1998;90(23):1810-6.
73. O'Connell M, Mailliard J, MacDonald J, Hailer D, Mayer R, Wieand H. An intergroup trial of intensive course 5-FU and low dose leucovorin as surgical adjuvant therapy for high risk colon cancer. *Proc Am Soc Clin Oncol*. 1993;12:190.
74. Panetti FJ, Goodman PJ, Costanzi JJ, Cruz AB, Vaitkevicius VK, McCracken JD, Brownlee RW, Laufman L, Stephens RL, Bonnet J. Adjuvant therapy in large bowel adenocarcinoma: long-term results of a Southwest Oncology Group Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1988;6(6):947-54.
75. Quasar Collaborative Group, Gray R, Barnwell J, McConkey C, Hills RK, Williams NS, Kerr DJ. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. *Lancet*. 2007;370(9604):2020-9.
76. QUASAR. Comparison of fluorouracil with additional levamisole, higher-dose folinic acid, or both, as adjuvant chemotherapy for colorectal cancer: a randomised trial. QUASAR Collaborative Group. *Lancet (London, England)*. 2000;355(9215):1588-96.
77. Rougier P, Sahmoud T, Nitti D, Curran D, Doci R, De Waele B, Nakajima T, Rauschecker H, Labianca R, Pector JC, Marsoni S, Apolone G, Lasser P, Couvreur ML, Wils J. Adjuvant portal-vein infusion of fluorouracil and heparin in colorectal cancer: a randomised trial. European Organisation for Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group, the Gruppo Interdisciplinare Valutazione Interventi in Oncologia, and the Japanese Foundation for Cancer Research. *Lancet*. 1998;351(9117):1677-81.
78. Rousselot LM, Cole DR, Grossi CE, Conte AJ, Gonzalez EM, Pasternack BS. Adjuvant chemotherapy with 5-fluorouracil in surgery for colorectal cancer: eight-year progress report. *Diseases of the colon and rectum*. 1972;15(3):169-74.
79. Sadahiro S, Suzuki T, Ishikawa K, Yasuda S, Tajima T, Makuuchi H, Saitoh T, Murayama C. Prophylactic hepatic arterial infusion chemotherapy for the prevention of liver metastasis in patients with colon carcinoma: a randomized control trial. *Cancer*. 2004;100(3):590-7.
80. Sakamoto J, Hamada C, Rahman M, Kodaira S, Ito K, Nakazato H, Ohashi Y, Yasutomi M. An individual patient data meta-analysis of adjuvant therapy with capecitabine in patients with curatively resected colon cancer. *Japanese journal of clinical oncology*. 2005;35(9):536-44.
81. Sakamoto J, Ohashi Y, Hamada C, Buyse M, Burzykowski T, Piedbois P, Meta-Analysis Group of the Japanese Society for Cancer of the Colon and Rectum, Meta-Analysis Group in Cancer. Efficacy of oral adjuvant therapy after resection of colorectal cancer: 5-year results from three randomized trials. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2004;22(3):484-92.
82. Sargent DJ, Goldberg RM, Jacobson SD, Macdonald JS, Labianca R, Haller DG, Shepherd LE, Seitz JF, Francini G. A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. *The New England journal of medicine*. 2001;345(15):1091-7.
83. Scheithauer W, Kornek G, Rosen H, Sebesta C, Marcell A, Kwasny W, Karall M, Depisch D. Combined intraperitoneal plus intravenous chemotherapy after curative resection for colonic adenocarcinoma. *European journal of cancer (Oxford, England : 1990)*. 1995;31A(12):1981-6.
84. Schippinger W, Samonigg H, Schaberl-Moser R, Greil R, Thödtmann R, Tschmelitsch J, Jagoditsch M, Steger GG, Jakesz R, Herbst F, Hofbauer F, Rabl H, Wohlmuth P, Gnant M, Thaler J, Austrian Breast and Colorectal Cancer Study Group. A prospective randomised phase III trial of adjuvant chemotherapy with 5-fluorouracil and leucovorin in patients with stage II colon cancer. *British journal of cancer*. 2007;97(8):1021-7.
85. Sparsø BH, Von der Maase H, Kristensen D, Christiansen J, Damgaard Nielsen SA, Hebjørn M, Andersen B. Complications following postoperative combined radiation and chemotherapy in adenocarcinoma of the rectum and rectosigmoid. A randomized trial that failed. *Cancer*. 1984;54(11):2363-6.

86. SWOG 8415/INT-0153. Poplin E, Benedetti J, Estes N. Phase III randomized trial of bolus 5-FU/leucovorin/levamisole versus 5-FU continuous infusion/levamisole as adjuvant therapy for high risk colon cancer (SWOG 8415/INT-0153). *Proc Am Soc Clin Oncol*. 2000;19:240a.
87. Taal BG, Van Tinteren H, Zoetmulder FA, NACCP group. Adjuvant 5FU plus levamisole in colonic or rectal cancer: improved survival in stage II and III. *British journal of cancer*. 2001;85(10):1437-43.
88. Taylor I, Machin D, Mullee M, Trotter G, Cooke T, West C. A randomized controlled trial of adjuvant portal vein cytotoxic perfusion in colorectal cancer. *The British journal of surgery*. 1985;72(5):359-63.
89. Vaillant JC, Nordlinger B, Deuffic S, Arnaud JP, Pelissier E, Favre JP, Jaeck D, Fourtanier G, Grandjean JP, Marre P, Letoublon C. Adjuvant intraperitoneal 5-fluorouracil in high-risk colon cancer: A multicenter phase III trial. *Annals of surgery*. 2000;231(4):449-56.
90. Verhaegen H. Levamisole therapy in patients with colorectal cancer. *Immunotherapy of human cancer*. 1982;
91. Vermorken JB, Claessen AM, van Tinteren H, Gall HE, Ezinga R, Meijer S, Scheper RJ, Meijer CJ, Bloemena E, Ransom JH, Hanna MG, Pinedo HM. Active specific immunotherapy for stage II and stage III human colon cancer: a randomised trial. *Lancet*. 1999;353(9150):345-50.
92. Veterans Administration Adjuvant Cancer Chemotherapy Cooperative Group. The use of 5-fluorodeoxyuridine (FUDR) as a surgical adjuvant in carcinoma of the stomach and colorectum. *Arch Surg*. 1963;86:926-31.
93. Wan XB, Pan ZZ, Chen G, Li LR, Wan DS. [Meta-analysis of postoperative adjuvant chemotherapy for Dukes' B colorectal carcinoma]. *Ai zheng = Aizheng = Chinese journal of cancer*. 2005;24(5):600-4.
94. Watanabe M, Kodaira S, Takahashi T, Tominaga T, Hojo K, Kato T, Kunitomo K, Isomoto H, Ohashi Y, Yasutomi M. Randomized trial of the efficacy of adjuvant chemotherapy for colon cancer with combination therapy incorporating the oral pyrimidine 1-hexylcarbamoyl-5-fluorouracil. *Langenbeck's archives of surgery / Deutsche Gesellschaft für Chirurgie*. 2006;391(4):330-7.
95. Watanabe M, Nishida O, Kunii Y, Kodaira S, Takahashi T, Tominaga T, Hojo K, Kato T, Niimoto M, Kunitomo K, Isomoto H, Ohashi Y, Yasutomi M. Randomized controlled trial of the efficacy of adjuvant immunochemotherapy and adjuvant chemotherapy for colorectal cancer, using different combinations of the intracutaneous streptococcal preparation OK-432 and the oral pyrimidines 1-hexylcarbamoyl-5-fluorouracil and uracil/tegafur. *International journal of clinical oncology / Japan Society of Clinical Oncology*. 2004;9(2):98-106.
96. Wereldsma JC, Bruggink ED, Meijer WS, Roukema JA, van Putten WL. Adjuvant portal liver infusion in colorectal cancer with 5-fluorouracil/heparin versus urokinase versus control. Results of a prospective randomized clinical trial (colorectal adenocarcinoma trial I). *Cancer*. 1990;65(3):425-32.
97. Windle R, Bell PR, Shaw D. Five year results of a randomized trial of adjuvant 5-fluorouracil and levamisole in colorectal cancer. *The British journal of surgery*. 1987;74(7):569-72.
98. Wolmark N, Rockette H, Fisher B, et al.. Leucovorinmodulated 5-FU (LV-FU) as adjuvant therapy for primary colon cancer. *Proc Am Soc Clin Oncol*. 1993;12:197.
99. Wunderlich M, Schiessel R, Rainer H, Rauhs R, Kovats E, Schemper M, Dittrich C, Micksche M, Sedlacek HH. Effect of adjuvant chemo- or immunotherapy on the prognosis of colorectal cancer operated for cure. *The British journal of surgery*. 1985;72 Suppl:S107-10.
100. Zalcberg JR, Siderov J, Simes J. The role of 5-fluorouracil dose in the adjuvant therapy of colorectal cancer. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 1996;7(1):42-6.
101. Zaniboni A, Erlichman C, Seitz JF. FUFA increases disease-free survival in resected B2C colon cancer: results of a pooled analysis of 3 randomised trials. *Proc Am Soc Clin Oncol*. 1993;12:191.
102. Zaniboni A, Labianca R, Marsoni S, Torri V, Mosconi P, Grilli R, Apolone G, Cifani S, Tinazzi A. GIVIO-SITAC 01: A randomized trial of adjuvant 5-fluorouracil and folinic acid administered to patients with colon carcinoma--long term results and evaluation of the indicators of health-related quality of life. *Gruppo Italiano Valutazione Interventi in Oncologia. Studio Italiano Terapia Adjuvante Colon. Cancer*. 1998;82(11):2135-44.