

Bölüm 3

TANI ANINDA UNREZEKTABL METASTAZI OLAN KOLOREKTAL KANSER OLGULARINDA PRİMER TÜMÖRÜN REZEKSİYONU

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GİRİŞ

Kolorektal kanserler dünyada ve ülkemizde erkeklerde ve kadınlarda 3. en sık görülen kanser türüdür. Ülkemizde 2014 verilerine göre erkeklerde 22.8/100.000 kişide görülürken, kadınlarda 13.8/100.000 kişide görülmektedir. Dünya verilerine benzer şekilde ülkemizde de kolorektal kanser tanısı alan hastaların %23 gibi önemli bir kısmı tanı anında karaciğer, akciğer, retroperitoneal lenf nodları ya da periton gibi uzak organlara metastaz yapmış olarak bulunmaktadır (1, 2).

TEDAVİ YAKLAŞIMLARI

Bilindiği üzere kolorektal kanserlerde temel tedavi yöntemi tümörlü segment onkolojik cerrahi prensiplere uygun şekilde rezeksyonudur. Senkron metastazı olan hastalarda ise uzak metastaz bölgesinin eş zamanlı ya da aşamalı rezeksyonu öncelikli olarak önerilmektedir (3, 4). Fakat kolorektal kanser senkron metastazlarının tanı anında büyük oranda (%75-90) unrezektabl olduğu da kabul edilmesi gereken bir gerçektir (5). Çokunlukla tam şifa beklenmeyen bu hasta grubunda öncelikle sistemik kemoterapi verilip komplikasyona göre mi cerrahi düşünülsün yoksa öncelikle primer tümörün rezeksyonu yapılp sistemik tedaviye devam mı edilsin hususunda kararsızlık söz konusudur. Amerikan kanser kılavuzu (NCCN) ve Avrupa Tıbbi Onkoloji Derneği (ESMO) kılavuzlarında sadece primer kolorektal kanser ilişkili obstrüksiyon, kanama, perforasyon ya da ciddi ağrı gibi durumlarda primer tümör rezeksyonu önerilse de vakaların yaklaşık %80 gibi çoğunluğunu oluşturan asemptomatik primer tümörü olan hastalarda uygun tedavi sıralamasının belirlenmesi açısından literatürde tartışmanın devam ettiği görülmektedir (6-35).

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cerrahi müdahale çoğu zaman kaçınılmazdır. Asemptomatik hastalarda tedavi modalitelerine karar verme konusunda ise modern, hedefe yönelik kemoterapötiklerin uygulandığı günümüzde, metodolojik kısıtlamaların minimalize edildiği, çok merkezli, geniş hasta popülasyonları üzerinde gerçekleştirilmiş randomize kontrollü çalışmaların sonuçlarına ihtiyaç duyulmaktadır. Halihazırda devam etmekte olan çalışmaların (Tablo 1) sonuçları hem sağkalım hem de yaşam kalitesi açısından bu tür hastalara yaklaşımımızı belirlemede faydalı olabilir.

Tablo 1. Devam Eden Randomize Kontrollü Çalışmalar

Çalışma ismi	Kayıt numarası*	Birincil amaç	Örneklem büyüklüğü	Tahmini bitiş tarihi
CR4 (56)	NCT02015923	KÖS, 2 yıl	346	Kasım 2018
GRECCAR 8 (57)	NCT02314182	GS, 3 yıl	290	Aralık 2018
Çin çok merkezli**	NCT02149784	GS, 3 yıl	480	Temmuz 2019
SYNCRONOUS (58)	ISRCTN30964555	GS, 3 yıl	800	Aralık 2019
JCOG1007**	UMIN000008147	GS	770	Aralık 2020
CAIRO4 (59)	NCT01606098	GS, 5 yıl	360	Ağustos 2021

*Kayıtlı olduğu veri tabanı kayıt numarası. NCT: www.Clinicaltrials.gov, ISRCTN: www.isrctn.com, UMIN: www.umin.ac.jp/ctr**Yayınlanmış çalışma protokollerini bulunmamaktadır. KÖS: Kansere özgü sağkalım, GS: Genel sağkalım

KAYNAKLAR

- Türkiye Kanser İstatistikleri (2014). (25.01.2019 tarihinde https://hsgm.saglik.gov.tr/depo/birimler/kanser-db/istatistik/2014-RAPOR._uzuun.pdf adresinden erişim sağlanmıştır)
- Cancer Stat Facts: ColorectalCancer (2018). (25.01.2019 tarihinde <https://seer.cancer.gov/statfacts/html/colorect.html> adresinden erişim sağlanmıştır)
- National Comprehensive Cancer Network. Colon Cancer (Version 4.2018)(25.01.2019 tarihinde https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf adresinden erişim sağlanmıştır)
- Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, Aranda Aguilar E, Bardelli A, Benson A, Bodoky G, Ciardiello F, D'Hoore A, Diaz-Rubio E, Douillard JY, Ducreux M, Falcone A, Grothey A, Gruenberger T, Haustermans K, Heinemann V, Hoff P, Köhne CH, Labianca R, Laurent-Puig P, Ma B, Maughan T, Muro K, Normanno N, Österlund P, Oyen WJ, Papamichael D, Pentheroudakis G, Pfeiffer P, Price TJ, Punt C, Ricke J, Roth A, Salazar R, Scheithauer W, Schmoll HJ, Tabernero J, Taïeb J, Tejpar S, Wasan H, Yoshino T, Zaanan A, Arnold D. (2016) ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann

- Oncol, 27(8), 1386-422
- Cook AD, Single R, McCahill LE. (2005) Surgical resection of primary tumors in patients who present with stage IV colorectal cancer: An analysis of surveillance, epidemiology, and results data, 1988 to 2000 Ann Surg Oncol, 12, 637–645
- Galizia G, Lieto E, Orditura M, Castellano P, Imperatore V, Pinto M, Zamboli A. (2008) First-line chemotherapy vs. bowel tumor resection plus chemotherapy for patients with unresectable synchronous colorectal hepatic metastases Arch Surg, 143(4), 352-8. doi: 10.1001/archsurg.143.4.352.
- Bajwa A, Blunt N, Vyas S, Suliman I, Bridgewater J, Hochhauser D, Ledermann JA, O'Byrne A. (2009) Primary tumour resection and survival in the palliative management of metastatic colorectal cancer. Eur J Surg Oncol, 35(2), 164-7. doi: 10.1016/j.ejso.2008.06.005.
- Ishihara S, Nishikawa T, Tanaka T, Tanaka J, Kiyomatsu T, Kawai K, Hata K, Nozawa H, Kazama S, Yamaguchi H, Sunami E, Kitayama J, Sugihara K, Watanabe T. (2015) Benefit of primary tumor resection in stage IV colorectal cancer with unresectable metastasis: a multicenter retrospective study using a propensity score analysis. Int J Colorectal Dis, 30(6), 807-12. doi: 10.1007/s00384-015-2228-4.
- Benoist S, Pautrat K, Mitry E, Rougier P, Penna C, Nordlinger B. (2005) Treatment strategy for patients with colorectal cancer and synchronous irresectable liver metastases. Br J Surg, 92(9), 1155-60.
- Ruo L, Gougoutas C, Paty PB, Guillem JG, Cohen AM, Wong WD. (2003) Elective bowel resection for incurable stage IV colorectal cancer: prognostic variables for asymptomatic patients. J Am Coll Surg, 196(5), 722-8.
- Stelzner S, Hellmich G, Koch R, Ludwig K.J. (2005) Factors predicting survival in stage IV colorectal carcinoma patients after palliative treatment: a multivariate analysis. Surg Oncol, 89(4), 211-7.
- Ferrand F, Malka D, Bourredjem A, Allonier C, Bouché O, Louafi S, Boige V, Mousseau M, Raoul JL, Bedenne L, Leduc B, Deguiral P, Faron M, Pignon JP, Ducreux M (2013) Impact of primary tumour resection on survival of patients with colorectal cancer and synchronous metastases treated by chemotherapy: results from the multicenter, randomized trial Fédération Francophone de Cancérologie Digestive 9601. Eur J Cancer, 49(1), 90-7. doi: 10.1016/j.ejca.2012.07.006.
- Gulack BC, Nussbaum DP, Keenan JE, Ganapathi AM, Sun Z, Worni M, Migaly J, Mantyh CR. (2016) Surgical Resection of the Primary Tumor in Stage IV Colorectal Cancer Without Metastasectomy is Associated With Improved Overall Survival Compared With Chemotherapy/Radiation Therapy Alone. Dis Colon Rectum, 59(4), 299-305. doi: 10.1097/DCR.0000000000000546.
- Aslam MI, Kelkar A, Sharpe D, Jameson JS. (2010) Ten years experience of managing the primary tumors in patients with stage IV colorectal cancers. Int J Surg, 8(4), 305-13. doi: 10.1016/j.ijsu.2010.03.005.
- Seo GJ, Park JW, Yoo SB, Kim SY, Choi HS, Chang HJ, Shin A, Jeong SY, Kim DY, Oh JH. (2010) Intestinal complications after palliative treatment for asymptomatic patients with unresectable stage IV colorectal cancer. Surg Oncol, 102(1), 94-9. doi: 10.1002/jso.21577.
- Karoui M, Roudot-Thoraval F, Mesli F, Mitry E, Aparicio T, Des Guetz G, Louvet C, Landi B, Tiret E, Sobhani I. (2011) Primary colectomy in patients with stage IV colon cancer and unresectable distant metastases improves overall survival: results of a mul-

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- ticentric study. *Dis Colon Rectum*, 54(8), 930-8. doi: 10.1097/DCR.0b013e31821cced0.
- Poultsides GA, Servais EL, Saltz LB, Patil S, Kemeny NE, Guillem JG, Weiser M, Temple LK, Wong WD, Paty PB. (2009) Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment. *J Clin Oncol*, 27(20), 3379-84. doi: 10.1200/JCO.2008.20.9817.
- Tsang WY, Ziogas A, Lin BS, Seery TE, Karnes W, Stamos MJ, Zell JA. (2014) Role of primary tumor resection among chemotherapy treated patients with synchronous stage IV colorectal cancer: a survival analysis. *J Gastrointest Surg*, 18(3), 592-8. doi: 10.1007/s11605-013-2421-0.
- Yun JA, Huh JW, Park YA, Cho YB, Yun SH, Kim HC, Lee WY, Chun HK. (2014) The role of palliative resection for asymptomatic primary tumor in patients with unresectable stage IV colorectal cancer. *Dis Colon Rectum*, 57(9), 1049-58. doi: 10.1097/DCR.0000000000000193.
- Ahmed S, Leis A, Chandra-Kanthan S, Fields A, Reeder B, Iqbal N, Haider K, Le D, Pahwa P. (2016) Surgical Management of the Primary Tumor in Stage IV Colorectal Cancer: A Confirmatory Retrospective Cohort Study. *J Cancer*, 7(7), 837-45. doi: 10.7150/jca.14717.
- Alawadi Z, Phatak UR, Hu CY, Bailey CE, You YN, Kao LS, Massarweh NN, Feig BW, Rodriguez-Bigas MA, Skibber JM, Chang GJ. (2017) Comparative effectiveness of primary tumor resection in patients with stage IV colon cancer. *Cancer*, 123(7), 1124-1133. doi: 10.1002/cncr.30230.
- Boselli C, Renzi C, Gemini A, Castellani E, Trastulli S, Desiderio J, Corsi A, Barberini F, Cirocchi R, Santoro A, Parisi A, Redler A, Noya G. (2013) Surgery in asymptomatic patients with colorectal cancer and unresectable liver metastases: the authors' experience. *Onco Targets Ther*, 6, 267-72. doi: 10.2147/OTT.S39448.
- Gresham G, Renouf DJ, Chan M, Kennecke HF, Lim HJ, Brown C, Cheung WY. (2014) Association between palliative resection of the primary tumor and overall survival in a population-based cohort of metastatic colorectal cancer patients. *Ann Surg Oncol*, 21(12), 3917-23. doi: 10.1245/s10434-014-3797-0.
- Kim MS, Chung M, Ahn JB, Kim CW, Cho MS, Shin SJ, Baek SJ, Hur H, Min BS, Baik SH, Kim NK. (2014) Clinical significance of primary tumor resection in colorectal cancer patients with synchronous unresectable metastasis. *J Surg Oncol*, 110(2), 214-21. doi: 10.1002/jso.23607.
- Miyamoto Y, Watanabe M, Sakamoto Y, Shigaki H, Murata A, Sugihara H, Etoh K, Ishimoto T, Iwatsuki M, Baba Y, Iwagami S, Yoshida N, Baba H. (2014) Evaluation of the necessity of primary tumor resection for synchronous metastatic colorectal cancer. *Surg Today*, 44(12), 2287-92. doi: 10.1007/s00595-014-0869-5.
- Niitsu H, Hinoi T, Shimomura M, Egi H, Hattori M, Ishizaki Y, Adachi T, Saito Y, Mignuchi M, Sawada H, Kochi M, Mukai S, Ohdan H. (2015) Up-front systemic chemotherapy is a feasible option compared to primary tumor resection followed by chemotherapy for colorectal cancer with unresectable synchronous metastases. *World J Surg Oncol*, 24, 13, 162. doi: 10.1186/s12957-015-0570-1.
- Park JH, Kim TY, Lee KH, Han SW, Oh DY, Im SA, Kang GH, Chie EK, Ha SW, Jeong SY, Park KJ, Park JG, Kim TY. (2013) The beneficial effect of palliative resection in metastatic colorectal cancer. *Br J Cancer*, 108(7), 1425-31. doi: 10.1038/bjc.2013.94.
- Kim SK, Lee CH, Lee MR, Kim JH. (2012) Multivariate Analysis of the Survival

- val Rate for Treatment Modalities in Incurable Stage IV Colorectal Cancer. *J Korean SocColoproctol*, 28(1), 35-41. doi: 10.3393/jksc.2012.28.1.35.
- ‘t Lam-Boer J, Van der Geest LG, Verhoef C, Elferink ME, Koopman M, de Wilt JH. (2016) Palliative resection of the primary tumor is associated with improved overall survival in incurable stage IV colorectal cancer: A nationwide population-based propensity-score adjusted study in the Netherlands. *Int J Cancer*, 139(9), 2082-94. doi: 10.1002/ijc.30240.
- Tanoue Y, Tanaka N, Nomura Y. (2010) Primary site resection is superior for incurable metastatic colorectal cancer. *World J Gastroenterol*, 16(28), 3561-6.
- Venderbosch S, de Wilt JH, Teerenstra S, Loosveld OJ, van Bochove A, Sinnige HA, Creemers GJ, Tesselaar ME, Mol L, Punt CJ, Koopman M. (2011) Prognostic value of resection of primary tumor in patients with stage IV colorectal cancer: retrospective analysis of two randomized studies and a review of the literature. *Ann SurgOncol*, 18(12), 3252-60. doi: 10.1245/s10434-011-1951-5.
- Verberne CJ, de Bock GH, Pijl ME, Baas PC, Siesling S, Wiggers T. (2012) Palliative resection of the primary tumour in stage IV rectal cancer. *Colorectal Dis*, 14(3), 314-9. doi: 10.1111/j.1463-1318.2011.02618.x.
- Wang Z, Liang L, Yu Y, Wang Y, Zhuang R, Chen Y, Cui Y, Zhou Y, Liu T. (2016) Primary Tumour Resection Could Improve the Survival of Unresectable Metastatic Colorectal Cancer Patients Receiving Bevacizumab-Containing Chemotherapy. *Cell PhysiolBiochem*, 39(3), 1239-46. doi: 10.1159/000447829.
- Wong SF, Wong HL, Field KM, Kosmider S, Tie J, Wong R, Tacey M, Shapiro J, Nott L, Richardson G, Cooray P, Jones I, Croxford M, Gibbs P. (2016) Primary Tumor Resection and Overall Survival in Patients With Metastatic Colorectal Cancer Treated With Palliative Intent. *Clin Colorectal Cancer*, 15(3), e125-32. doi: 10.1016/j.clcc.2015.12.010
- Yoon YS, Kim CW, Lim SB, Yu CS, Kim SY, Kim TW, Kim MJ, Kim JC. (2014) Palliative surgery in patients with unresectable colorectal liver metastases: a propensity score matching analysis. *J SurgOncol*, 109(3), 239-44. doi: 10.1002/jso.23480.
- van der Burg ME, van Lent M, Buyse M, Kobierska A, Colombo, N, Favalli G, Lacave AJ, Nardi M, Renard J, Pecorelli S. (1995) The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. *Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer*. *N Engl J Med*, 332, 629-634
- Flanigan RC, Salmon SE, Blumenstein BA, Bearman SI, Roy V, McGrath PC, Caton JR, Munshi N, Crawford ED. (2001) Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med*, 345, 1655-1659
- Durante C, Boukheris H, Dromain C, et al. (2009) Prognostic factors influencing survival from metastatic (stage IV) gastroenteropancreatic well-differentiated endocrine carcinoma. *Endocr Relat Cancer*, 16(2), 585-97.
- Wilkinson KJ, Chua W, Ng W, Roohullah A. (2015) Management of asymptomatic primary tumours in stage IV colorectal cancer: Review of outcomes. *World J Gastrointestinal Oncol*, 7(12), 513-23. doi: 10.4251/wjgo.v7.i12.513.
- Karoui M, Soprani A, Charachon A, et al. (2010) Primary chemotherapy with or without colonic stent for management of unresectable stage IV colorectal cancer. *Eur J Surg Oncol*, 36(1), 58-64.
- Cirocchi R, Farinella E, Trastulli S, et al. (2013) Safety and efficacy of endoscopic colo-

- nic stenting as a bridge to surgery in the management of intestinal obstruction due to left colon and rectal cancer: a systematic review and meta-analysis. *SurgOncol*, 22(1), 14–21.
- Søreide K. (2013) Emergency management of acute obstructed left-sided colon cancer: loops, stents or tubes? *Endoscopy*, 45(4), 247–8. doi: 10.1055/s-0032-1326404.
- Cirocchi R, Trastulli S, Abraha I, Vettoretto N, Boselli C, Montedori A, Parisi A, Noya G, Platell C. (2012) Non-resection versus resection for an asymptomatic primary tumour in patients with unresectable stage IV colorectal cancer. *Cochrane Database Syst Rev*, Aug 15;(8):CD008997. doi: 10.1002/14651858.CD008997.pub2.
- Clancy C, Burke JP, Barry M, Kalady MF, Calvin Coffey J. (2014) A meta-analysis to determine the effect of primary tumor resection for stage IV colorectal cancer with unresectable metastases on patient survival. *Ann SurgOncol*, 21(12), 3900–8. doi: 10.1245/s10434-014-3805-4
- deGramont A, Figer A, Seymour Met al. (2000) Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J ClinOncol*, 18, 2938–2947.
- Tournigand C, Andre T, Achille E et al. (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J ClinOncol*, 22, 229–237.
- Hurwitz H, Fehrenbacher L, Novotny W et al. (2004) Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*, 350, 2335–2342.
- Kabbinavar FF, Hambleton J, Mass RD et al. (2005) Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. *J ClinOncol*, 23, 3706–3712.
- Giantonio BJ, Catalano PJ, Meropol NJ et al. (2007) Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J ClinOncol*, 25, 1539–1544.
- Cunningham D, Humblet Y, Siena S et al. (2004) Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med*, 351, 337–345.
- Sobrero AF, Maurel J, Fehrenbacher L et al. (2008) EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. *J ClinOncol*, 26, 2311–2319.
- Kodaz H, Erdogan B, Hacibekiroglu I, Turkmen E, Tozkir H, Albayrak D, Uzunoglu S, Cicin I. (2015) Primary Tumor Resection Offers Higher Survival Advantage in KRAS Mutant Metastatic Colorectal Cancer Patients. *Hepatogastroenterology*, 62(140), 876–9.
- Ha GW, Kim JH, Lee MR. (2018) Meta-analysis of oncologic effect of primary tumor resection in patients with unresectable stage IV colorectal cancer in the era of modern systemic chemotherapy. *Ann Surg Treat Res*, 95(2), 64–72. doi: 10.4174/str.2018.95.2.64.
- Maciver AH, Lee N, Skitzki JJ, Boland PM, Francescutti V. (2017) Cytoreduction and hyperthermic intraperitoneal chemotherapy (CS/HIPEC) in colorectal cancer: Evidence-based review of patient selection and treatment algorithms. *Eur J SurgOncol*, 43(6), 1028–1039. doi: 10.1016/j.ejso.2016.09.012.
- Morikawa T, Inada R, Nagasaka T, Mori Y, Kishimoto H, Kawai T, Umeda Y, Mishima H, Goel A, Fujiwara T. (2018) BRAF V600E mutation is a predictive indica-

- tor of upfront chemotherapy for stage IV colorectal cancer. *Oncol Lett*, 15(2), 2195-2201. doi: 10.3892/ol.2017.7553.
- Biondo S, Frago R, Kreisler E, Espin-Basany E, Spanish CRG. (2017) Impact of resection versus no resection of the primary tumor on survival in patients with colorectal cancer and synchronous unresectable metastases: protocol for a randomized multicenter study (CR4). *Int J Colorectal Dis*, 32, 1085–90.
- Cotte E, Villeneuve L, Passot G, Boschetti G, Bin-Dorel S, Francois Y, Glehen O. (2015) GRECCAR 8: impact on survival of the primary tumor resection in rectal cancer with unresectable synchronous metastasis: a randomized multicenter study. *BMC Cancer*, 15, 1.
- Rahbari NN, Lordick F, Fink C, Bork U, Stange A, Jäger D, Luntz SP, Englert S, Rossion I, Koch M. (2012) Resection of the primary tumour versus no resection prior to systemic therapy in patients with colon cancer and synchronous unresectable metastases (UICC stage IV): SYNCHRONOUS-a randomised controlled multicentre trial (ISR-CTN30964555). *BMC Cancer*, 12, 142.
- Mol L, Verhoef C, de Haan AF, Yilmaz M, Punt CJ, de Wilt JH, Koopman M. (2014) The CAIRO4 study: the role of surgery of the primary tumour with few or absent symptoms in patients with synchronous unresectable metastases of colorectal cancer—a randomized phase III study of the Dutch Colorectal Cancer Group (DCCG). *BMC Cancer*, 14, 741.