



BÖLÜM 36

Rektum Kanserinde Neoadjuvan ve Adjuvan Tedavi

Halil ÇELİK¹
Emel SEZER²

Giriş

Amerika Birleşik Devletleri’nde (ABD) her yıl yaklaşık 45.230 hastaya rektum kanseri teşhisi konmaktadır (1). Rektal adenokarsinomda cerrahi rezeksiyon küratif tedavinin temel taşıdır, ancak tek başına cerrahi, yalnızca erken evre hastalığı (evre 1) olan hastalar için yüksek kür oranı sağlar. Birçok randomize çalışmada, ameliyattan önce ve sonra kemoterapi (KT) ve radyoterapi (RT) eklenerken sonuçlar iyileştirmeye çalışılmıştır. RT, kolon kanserine göre, rezeksiyonu takiben daha yüksek oranda lokal nüks olması nedeniyle, rektum kanseri için önemli bir tedavi bileşeni olarak ortaya çıkmıştır (2).

Çok nadir görülen primer rektal skuamöz hücreli karsinomların anal kanserlerden ayırt edilmesi bazen zor olabilir ve anal kanserle aynı yaklaşımla, yani cerrahi yerine öncelikle kemoradyoterapi (KRT) ile tedavi edilir (3).

Yüzeysel küçük invaziv rektal adenokarsinomlar, lokal eksizyon gibi sınırlı cerrahi prosedürlerle etkili bir şekilde tedavi edilebilir. Bununla birlikte, hastaların çoğu, LAR (Low anterior rezeksiyon) veya APR (Abdomino-perineal rezeksiyon) gibi daha kapsamlı transabdominal cerrahi gerektiren derin invaziv tümörlere sahiptir. Bazıları da, sakrum, pelvik yan duvarlar, prostat veya mesane gibi komşu doku ve organlara invaze olan lokal olarak ilerlemiş tümörler ile kendini gösterir. Bu hastaların cerrahi ve onkolojik yönetimi büyük ölçüde evresine ve rektum içindeki konumuna bağlı olarak değişir. Üst ve orta rektumdaki tümörler genellikle LAR, koloanal anastomoz ve anal sfinkterin korunması ile yönetilebilir. Ortaya çıkan anorektal fonksiyon kusurlu olsa da, pelvik otonom sinirlerin korunmasıyla postoperatif cinsel ve üriner disfonksiyon riski azaltılabilir. Bu operasyonlar, çoğu durumda, özellikle total mezorektal eksizyon (TME) ile beraber yapılmaktadır. Alt rektumdaki

¹ Uzm. Dr., Mersin Üniversitesi Tip Fakültesi, Tibbi Onkoloji Bilim Dalı, halil.celik.3363@gmail.com

² Prof. Dr., Mersin Üniversitesi Tip Fakültesi, Tibbi Onkoloji Bilim Dalı, emel.yaman@gmail.com

Kaynaklar

1. Siegel RL, Miller KD, Fuchs HE, et al. A. Cancer Statistics, 2021. CA Cancer J Clin. 2021;71:7-33.
2. Ma B, Gao P, Wang H, et al. What has preoperative radio (chemo) therapy brought to localized rectal cancer patients in terms of perioperative and long-term outcomes over the past decades? A systematic review and meta-analysis based on 41,121 patients. Int J Cancer. 2017;141:1052-1065.
3. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. 2001;345:638-646.
4. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology. (10/12/2021 tarihinde <https://www.nccn.org/professionals> adresinden ulaşılmıştır).
5. Gerard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol. 2006;24:4620-4625.
6. Bosset JF, Calais G, Mineur L, et al. Enhanced tumoricidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results EORTC 22921. J Clin Oncol. 2005;23:5620-5627.
7. Boulis-Wassif S, Gerard A, Loygue J, et al. Final results of a randomized trial on the treatment of rectal cancer with preoperative radiotherapy alone or in combination with 5-fluorouracil, followed by radical surgery. Trial of the European Organization on Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group. Cancer. 1984;53:1811-1818.
8. Ceelen WP, Van Nieuwenhove Y, Fierens K. Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer. Cochrane Database Syst Rev. 2009;CD006041.
9. McCarthy K, Pearson K, Fulton R, et al. Preoperative chemoradiation for non-metastatic locally advanced rectal cancer. Cochrane Database Syst Rev. 2012;12CD008368.
10. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351:1731-1740.
11. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AI0-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol. 2012;30:1926-1933.
12. Rödel C, Martus P, Papadopoulos T, et al. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. J Clin Oncol. 2005;23:8688-8696.
13. Fokas E, Liersch T, Fietkau R, et al. Tumor regression grading after preoperative chemoradiotherapy for locally advanced rectal carcinoma revisited: updated results of the CAO/ARO/AI0-94 trial. J Clin Oncol. 2014;32:1554-1562.
14. Chang GJ, Rodriguez-Bigas MA, Eng C, et al. Lymph node status after neoadjuvant radiotherapy for rectal cancer is a biologic predictor of outcome. Cancer. 2009;115:5432-5440.
15. Yeo SG, Kim DY, Kim TH, et al. Pathologic complete response of primary tumor following preoperative chemoradiotherapy for locally advanced rectal cancer: long-term outcomes and prognostic significance of pathologic nodal status (KROG 09-01). Ann Surg. 2010;252:998-1004.
16. Klos CL, Shellito PC, Rattner DW, et al. The effect of neoadjuvant chemoradiation therapy on the prognostic value of lymph nodes after rectal cancer surgery. Am J Surg. 2010;200:440-445.
17. Park IJ, You YN, Agarwal A, et al. Neoadjuvant treatment response as an early response indicator for patients with rectal cancer. J Clin Oncol. 2012;30:1770-1776.
18. Wheeler JM, Warren BF, Mortensen NJ, et al. Quantification of histologic regression of rectal cancer after irradiation: a proposal for a modified staging system. Dis Colon Rectum. 2002;45:1051-1056.
19. Vecchio FM, Valentini V, Minsky BD, et al. The relationship of pathologic tumor regression grade (TRG) and outcomes after preoperative therapy in rectal cancer. Int J Radiat Oncol Biol Phys. 2005;62:752-760.
20. Fokas E, Ströbel P, Fietkau R, et al. Tumor Regression Grading After Preoperative Chemoradiotherapy as a Prognostic Factor and Individual-Level Surrogate for Disease-Free Survival in Rectal Cancer. J Natl Cancer Inst. 2017;109.
21. Roh MS, Colangelo LH, O'Connell MJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol. 2009;27:5124-5130.
22. Park JH, Yoon SM, Yu CS, et al. Randomized phase 3 trial comparing preoperative and postoperative chemoradiotherapy with capecitabine for locally advanced rectal cancer. Cancer. 2011;117:3703-3712.
23. Mohiuddin M, Regine WF, John WJ, et al. Preoperative chemoradiation in fixed distal rectal cancer: dose time factors for pathological complete response. Int J Radiat Oncol Biol Phys. 2000;46:883-888.
24. Hojheinz RD, Wenz F, Post S, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. Lancet Oncol. 2012;13:579-588.
25. O'Connell MJ, Colangelo LH, Beart RW, et al. Capecitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer: surgical end points from National Surgical Adjuvant Breast and Bowel Project trial R-04. J Clin Oncol. 2014;32:1927-1934.
26. Allegra CJ, Yothers G, O'Connell MJ, et al. Neoadjuvant 5-FU or Capecitabine Plus Radiation With or Without Oxaliplatin in Rectal Cancer Patients: A Phase III Randomized Clinical Trial. J Natl Cancer Inst. 2015;107:dvj248.
27. Zou XC, Wang QW, Zhang JM. Comparison of 5-FU-based and Capecitabine-based Neoadju-

- vant Chemoradiotherapy in Patients With Rectal Cancer: A Meta-analysis. *Clin Colorectal Cancer.* 2017;16:e123-e139.
28. Gieschke R, Burger HU, Reigner B, et al. Population pharmacokinetics and concentration effect relationships of capecitabine metabolites in colorectal cancer patients. *Br J Clin Pharmacol.* 2003;55:252-263.
 29. Aschele C, Cionini L, Lonardi S, et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. *J Clin Oncol.* 2011;29:2773-2780.
 30. Gerard JP, Azria D, Gourgou-Bourgade S, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. *J Clin Oncol.* 2010;28:1638-1644.
 31. Gerard JP, Azria D, Gourgou-Bourgade S, et al. Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomized trial in rectal cancer. *J Clin Oncol.* 2012;30:4558-4565.
 32. Rödel C, Liersch T, Becker H, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AI0-04 randomised phase 3 trial. *Lancet Oncol.* 2012;13:679-687.
 33. Rödel C, Graeven U, Fietkau R, et al. Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AI0-04 study): final results of the multicentre, open label, randomised, phase 3 trial. *Lancet Oncol.* 2015;16:979-989.
 34. Jiao D, Zhang R, Gang Z, et al. Fluorouracil-based preoperative chemoradiotherapy with or without oxaliplatin for stage II/III rectal cancer: a 3-year follow-up study. *Chin J Cancer Res.* 2015;27:588-596.
 35. Haddad P, Miriae M, Farhan F, et al. Addition of oxaliplatin to neoadjuvant radiochemotherapy in MRI-defined T3, T4 or N+ rectal cancer: a randomized clinical trial. *Asia Pac J Clin Oncol.* 2017;13:416-422.
 36. Saha A, Ghosh SK, Roy C, et al. A randomized controlled pilot study to compare capecitabine-oxaliplatin with 5-FU-leucovorin as neo adjuvant concurrent chemoradiation in locally advanced adenocarcinoma of rectum. *J Cancer Res Ther.* 2015;11:88-93.
 37. Kayal PK, Saha A, Dastidar AG, et al. A randomized comparative study between neoadjuvant 5-fluorouracil and leucovorin versus 5-fluorouracil and cisplatin along with concurrent radiation in locally advanced carcinoma rectum. *Clin Cancer Invest J.* 2014;3:32-37.
 38. Deng Y, Chi P, Lan P, et al. Neoadjuvant Modified FOLFOX6 With or Without Radiation Versus Fluorouracil Plus Radiation for Locally Advanced Rectal Cancer: Final Results of the Chinese FOWARC Trial. *J Clin Oncol.* 2019;37:3223-3233.
 39. Schmoll Hl, Stein A, Van Cutsem E, et al. Pre and Postoperative Capecitabine Without or With Oxaliplatin in Locally Advanced Rectal Cancer: PETACC 6 Trial by EORTC GITCG and ROG, AIO, AGITG, BGDO, and FFCD. *J Clin Oncol.* 2021;39:17-29.
 40. Aschele C, Lonardi S, Cionini L, et al. Final results of STAR-01: A randomized phase III trial comparing preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer. *J Clin Oncol.* 2016;34S:ASCO#3521.
 41. Hüttner FJ, Probst P, Kalkum E, et al. Addition of Platinum Derivatives to Fluoropyrimidine-Based Neoadjuvant Chemoradiotherapy for Stage II/III Rectal Cancer: Systematic Review and Meta-Analysis. *J Natl Cancer Inst.* 2019;111:887-902.
 42. Navarro M, Dotor E, Rivera F, et al. A Phase II study of preoperative radiotherapy and concomitant weekly irinotecan in combination with protracted venous infusion 5-fluorouracil, for resectable locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys.* 2006;66:201-205.
 43. Willeke F, Horisberger K, Kraus-Tiefenbacher U, et al. A phase II study of capecitabine and irinotecan in combination with concurrent pelvic radiotherapy (Capri-RT) as neoadjuvant treatment of locally advanced rectal cancer. *Br J Cancer.* 2007;96:912-917.
 44. Gollins S, Sun Myint A, Haylock B, et al. Preoperative chemoradiotherapy using concurrent capecitabine and irinotecan in magnetic resonance imaging-defined locally advanced rectal cancer: impact on long-term clinical outcomes. *J Clin Oncol.* 2011;29:1042-1049.
 45. Mohiuddin M, Paulus R, Mitchell E, et al. Neoadjuvant chemoradiation for distal rectal cancer: 5-year updated results of a randomized phase 2 study of neoadjuvant combined modality chemoradiation for distal rectal cancer. *Int J Radiat Oncol Biol Phys.* 2013;86:523-528.
 46. Willett CG, Duda DG, di Tomaso E, et al. Efficacy, safety, and biomarkers of neoadjuvant bevacizumab, radiation therapy, and fluorouracil in rectal cancer: a multidisciplinary phase II study. *J Clin Oncol.* 2009;27:3020-3026.
 47. Crane CH, Eng C, Feig BW, et al. Phase II trial of neoadjuvant bevacizumab, capecitabine, and radiotherapy for locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys.* 2010;76:824-830.
 48. Uehara K, Hiramatsu K, Maeda A, et al. Neoadjuvant oxaliplatin and capecitabine and bevacizumab without radiotherapy for poor risk rectal cancer: N-SOG 03 Phase II trial. *Jpn J Clin Oncol.* 2013;43:964-971.
 49. Landry JC, Feng Y, Prabhu RS, et al. Phase II Trial of Preoperative Radiation With Concurrent Capecitabine, Oxaliplatin, and Bevacizumab Followed by Surgery and Postoperative 5-Fluorouracil, Leucovorin, Oxaliplatin (FOLFOX), and Bevacizumab in Patients With Locally Advanced Rectal Cancer: 5-Year Clinical Outcomes ECOG-ACRIN Cancer Research Group E3204. *Oncologist.* 2015;20:615-616.
 50. Fernandez-Martos C, Pericay C, Losa F, et al. Effect of Afibbercept Plus Modified FOLFOX6 Induction Chemotherapy Before Standard Chemoradiotherapy and Surgery in Patients With High Risk Rectal Adenocarcinoma: The GEMCAD 1402 Randomized Clinical Trial. *JAMA Oncol.* 2019;5:1566-1573.

51. Velenik V, Ocvirk J, Oblak I, et al. Aphase II study of cetuximab, capecitabine and radiotherapy in neoadjuvant treatment of patients with locally advanced resectable rectal cancer. *Eur J Surg Oncol.* 2010;36:244-250.
52. Horisberger K, Treschl A, Mai S, et al. Cetuximab in combination with capecitabine, irinotecan, and radiotherapy for patients with locally advanced rectal cancer: results of a Phase II MARGIT trial. *Int J Radiat Oncol Biol Phys.* 2009;74:1487-1493.
53. Dewdney A, Cunningham D, Tabernero J, et al. Multicenter randomized phase II clinical trial comparing neoadjuvant oxaliplatin, capecitabine, and preoperative radiotherapy with or without cetuximab followed by total mesorectal excision in patients with high-risk rectal cancer (EXPERT-C). *J Clin Oncol.* 2012;30:1620-1627.
54. Kim SY, Shim EK, Yeo HY, et al. KRAS mutation status and clinical outcome of preoperative chemoradiation with cetuximab in locally advanced rectal cancer: a pooled analysis of 2 phase II trials. *Int J Radiat Oncol Biol Phys.* 2013;85:201-207.
55. Helbling D, Bodoky G, Gautschi O, et al. Neoadjuvant chemoradiotherapy with or without panitumumab in patients with wild-type KRAS, locally advanced rectal cancer (LARC): a randomized, multicenter, phase II trial SAKK 41/07. *Ann Oncol.* 2013;24:718-725.
56. Sclafani F, Gonzalez D, Cunningham D, et al. TP53 mutational status and cetuximab benefit in rectal cancer: 5-year results of the EXPERT-C trial. *J Natl Cancer Inst.* 2014;106:dju121.
57. Cercek A, Dos Santos Fernandes G, Roxburgh CS, et al. Mismatch Repair Deficient Rectal Cancer and Resistance to Neoadjuvant Chemotherapy. *Clin Cancer Res.* 2020;26:3271-3279.
58. Garcia-Aguilar J, Chow OS, Smith DD, et al. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. *Lancet Oncol.* 2015;16:957-966.
59. Cercek A, Roxburgh CSD, Strombom P, et al. Adoption of Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer. *JAMA Oncol.* 2018;4:e180071.
60. Petrelli F, Trevisan F, Cabiddu M, et al. Total Neoadjuvant Therapy in Rectal Cancer: A Systematic Review and Meta-analysis of Treatment Outcomes. *Ann Surg.* 2020;271:440-448.
61. Petersen SH, Harling H, Kirkeby LT, et al. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. *Cochrane Database Syst Rev.* 2012;2012:CD004078.
62. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med.* 2006;355:1114-1123.
63. Bosset JF, Calais G, Mineur L, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: longterm results of the EORTC 22921 randomised study. *Lancet Oncol.* 2014;15:184-190.
64. Collette L, Bosset JF, den Dulk M, et al. Patients with curative resection of cT3-4 rectal cancer after preoperative radiotherapy or radiochemotherapy: does anybody benefit from adjuvant fluorouracil-based chemotherapy? A trial of the European Organisation for Research and Treatment of Cancer Radiation Oncology Group. *J Clin Oncol.* 2007;25:4379-4386.
65. Sainato A, Cernusco Luna Nunzia V, Valentini V, et al. No benefit of adjuvant Fluorouracil Leucovorin chemotherapy after neoadjuvant chemoradiotherapy in locally advanced cancer of the rectum (LARC): Long term results of a randomized trial (I-CNR-RT). *Radiother Oncol.* 2014;113:223-229.
66. Breugom Al, van Gijn W, Muller EW, et al. Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo) radiotherapy and total mesorectal excision: a Dutch Colorectal Cancer Group (DCCG) randomized phase III trial. *Ann Oncol.* 2015;26:696-701.
67. Swets M, Kuppen PJK, Blok EL, et al. Are pathological high-risk features in locally advanced rectal cancer a useful selection tool for adjuvant chemotherapy? *Eur J Cancer.* 2018;89:1-8.
68. Glynne-Jones R, Counsell N, Quirke P, et al. Chronicle: results of a randomised phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomising postoperative adjuvant capecitabine plus oxaliplatin (XELOX) versus control. *Ann Oncol.* 2014;25:1356-1362.
69. Breugom Al, Swets M, Bosset JF, et al. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. *Lancet Oncol.* 2015;16:200-207.
70. Up to date, Neoadjuvant chemoradiotherapy, radiotherapy, and chemotherapy for rectal adenocarcinoma. Graphic 131311 Version 1.0. (10/12/2021 tarihinde <https://www.uptodate.com> adresinden ulaşılmıştır).