BÖLÜM 28

İnce Bağırsak Adenokarsinomunda Tedavi

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Giriş

Gastrointestinal sistemin diğer kanserlerine göre ince bağırsak kanserleri %3 gibi daha nadir bir görülme sıklığına sahiptir (1).

İnce bağırsaktan kaynaklanan en sık görülen histolojik alt tipler ince bağırsak adenokarsinomları, nörendokrin tümörler, gastrointestinal stromal tümörler ve lenfomalardır. Bu grup içerisinde ince bağırsak adenokarsinomları (İBA) %30-40 oranında görülmektedir (2).

İnce bağırsak adenokarsinomları TNM (tümör, lenf nodu, metastaz) evreleme sistemine göre evrelenir (Tablo 1) (3).

Lokorejyonel Hastalıkta Tedavi

Cerrahi, potansiyel olarak küratif tek tedavi olmasına rağmen hastaların %40'ında primer tümör rezeksiyonu sonrası nüks görülmektedir (4). İBA için nüks paterni ağırlıklı olarak sistemiktir, retrospektif büyük bir çalışmada uzak ve lokal nüks sırasıyla tüm nükslerin %86 ve %18'ini oluşturmaktadır (5).

Lenf nodu pozitif vakalarda beş yıllık sağkalım düşük (%28-32) olmaktadır (4, 5). Lokal ileri İBA arasında (evre III, %21-27) lenf nodu tutulumunun derecesi ana prognostik faktördür. 5 yıllık hastalıksız sağkalım üç veya daha fazla lenf nodu pozitifliğinde iki veya daha az lenf nodu pozitifliğine kıyasla (5 yıllık hastalıksız sağkalım (disease free survival-DFS) oranları sırasıyla %37'ye karşı %58, P < 0,01) daha kötüdür (6).

Optimal perioperatif tedavide henüz belirlenmiş bir standart yoktur. Uluslararası faz III BALLAD çalışması halen devam etmekte olan ilk prospektif çalışmadır. Evre I-III İBA'lı hastalarda adjuvan 5-Fluorourasil/leucovorinin (5-FU/LV) veya 5-FU/LV artı oksaliplatinin (FOLFOX) tek başına gözlemle karşılaştırılması amaçlanmaktadır. Benzer bir çalışma da Japonya'da devam etmektedir. BALLAD çalışmasının sonuçları yayınlanana kadar İBA için adjuvan tedavinin yararı sadece retrospektif çalışmalara dayanmaktadır (7, 8).

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Tedavi Sonrası Gözlem

NCCN'den gelen yönergeler genellikle, bazı istisnalar dışında, rezeke edilmiş kolon kanserinde benzer bir yaklaşım izlemektedir ve aşağıda belirtildiği şekildedir (34).

- Öykü ve fizik muayene, 2 yıl boyunca her 3-6 ayda bir, daha sonra toplam 5 yıl boyunca her 6 ayda bir
- Toraks/karın/pelvik BT 2 yıl boyunca her 6-12 ayda bir, ardından toplam 5 yıl boyunca yılda bir
- Tümör belirteçlerinin testi karsinoembriyojenik antijen (CEA) ve/veya kanser antijeni 19-9 (CA 19-9) 2 yıl boyunca her 3-6 ayda bir, daha sonra toplam 5 yıl boyunca her 6 ayda bir
- Rutin kapsül endoskopisi endike değildir

Kaynaklar

1. Noone A, Howlader N, Krapcho M. SEER Cancer Statistics Review, 1975–2015; Based on November 2017 SEER data submission, posted to the SEER website April 2018; National Cancer Institute: Bethesda, MD, USA, 2018. 2019.
2. Locher C, Batumona B, Afchain P, et al. Small bowel adenocarcinoma: French intergroup clinical practice guidelines for diagnosis, treatments and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO). Dig Liver Dis. 2018;50(1):15-19.
3. Small Intestine Cancer (Adenocarcinoma) Stages. (2018). 12/12/2021 tarihinde https://www.cancer.org/cancer/small-intestine-cancer/detection-diagnosis-staging/staging.html adresinden ulaşılmıştır.
4. Talamonti MS, Goetz LH, Rao S, et al. Primary cancers of the small bowel: analysis of prognostic factors and results of surgical management. Arch Surg. 2002;137(5):564-571.
5. Dabaja BS, Suki D, Pro B, et al. Adenocarcinoma of the small bowel: presentation, prognostic factors, and outcome of 217 patients. Cancer. 2004;101(3):518-526.
6. Overman MJ, Hu CY, Wolff RA, et al. Prognostic value of lymph node evaluation in small bowel adenocarcinoma: analysis of the surveillance, epidemiology, and end results database. Cancer. 2010;116(23):5374-5382.
7. Benson AB, Venook AP, Al-Hawary MM, et al. Small bowel adenocarcinoma, version 1.2020, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2019;17(9):1109-1133.
8. Kitahara H, Honma Y, Ueno M, et al. Randomized phase III trial of post-operative chemotherapy for patients with stage I/II/III small bowel adenocarcinoma (JCOG1502C, J-BALLAD). Jpn J Clin Oncol. 2019;49(3):287-290.
9. Young JI, Mongoue-Tchokote S, Wieghard N, et al. Treatment and survival of small-bowel adenocarcinoma in the United States: A comparison with colon cancer. Dis Colon Rectum. 2016;59(4):306-315.
10. Ecker BL, McMillan MT, Datta J, et al. Efficacy of adjuvant chemotherapy for small bowel adenocarcinoma: a propensity score–matched analysis. Cancer. 2016;122(5):693-701.
11. Ye X, Zhang G, Chen H, et al. Meta-analysis of postoperative adjuvant therapy for small bowel adenocarcinoma. PloS one. 2018;13(8):e0200204.
12. Schwameis K, Schoppmann SF, Stift J, et al. Small bowel adenocarcinomaterra incognita: A demand for cross-national pooling of data. Oncol Lett. 2014;7(5):1613-1617.
13. Aydin D, Sendur MA, Kefeli U, et al. Evaluation of prognostic factors and adjuvant chemotherapy in patients with small bowel adenocarcinoma who underwent curative resection. Clin Colorectal Cancer. 2017;16(3):220-227.
14. Meijer LL, Alberga AJ, de Bakker JK, et al. Outcomes and treatment options for duodenal adenocarcinoma: a systematic review and meta-analysis. Ann Surg Oncol. 2018;25(9):2681-2692.
15. Bakaeen FG, Murr MM, Sarr MG, et al. What prognostic factors are important in duodenal adenocarcinoma? Arch Surg. 2000;135(6):635-642.
16. Agrawal S, McCarron EC, Gibbs JF, et al. Surgical management and outcome in primary adenocarcinoma of the small bowel. Ann Surg Oncol. 2007;14(8):2263-2269.
17. Moon YW, Rha SY, Shin SJ, et al. Adenocarcinoma of the small bowel at a single Korean institute: management and prognosticators. J Cancer Res Clin Oncol. 2010;136(3):387-394.
18. Bilimoria KY, Bentrem DJ, Wayne JD, et al. Small bowel cancer in the United States: changes in epidemiology, treatment, and survival over the last 20 years. Ann Surg. 2009;249(1):63-71.
19. Neoptolemos JP, Moore MJ, Cox TF, et al. Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma: the ESPAC-3 periampullary cancer randomized trial. JAMA. 2012;308(2):147-156.
20. Howe JR, Karnell LH, Menck HR, et al. Adenocarcinoma of the small bowel: review of the National Cancer Data Base, 1985–1995. Cancer. 1999;86(12):2693-2706.
21. Ecker BL, McMillan MT, Datta J, et al. Adjuvant chemotherapy versus chemoradiotherapy in the management of patients with surgically resected duodenal adenocarcinoma: A propensity score-matched analysis of a nationwide clinical oncology database. Cancer. 2017;123(6):967-976.

22. Sohn TA, Lillemoe KD, Cameron JL, et al. Adenocarcinoma of the duodenum: factors influencing long-term survival. J Gastrointest Surg. 1998;2(1):79-87.
23. Kelsey CR, Nelson JW, Willett CG, et al. Duodenal adenocarcinoma: patterns of failure after resection and the role of chemoradiotherapy. Int J Radiat Oncol Biol Phys. 2007;69(5):1436-1441.
24. Bree E, Rovers KP, Stamatiou D, et al. The evolving management of small bowel adenocarcinoma. Acta Oncol. 2018;57(6):712-722.
25. Poultsides GA, Huang LC, Cameron JL, et al. Duodenal adenocarcinoma: clinicopathologic analysis and implications for treatment. Ann Surg Oncol. 2012;19(6):1928-1935.
26. Coia L, Hoffman J, Scher R, et al. Preoperative chemoradiation for adenocarcinoma of the pancreas and duodenum. Int J Radiat Oncol Biol Phys. 1994;30(1):161-167.
27. Yeung RS, Weese JL, Hoffman JP, et al. Neoadjuvant chemoradiation in pancreatic and duodenal carcinoma. A phase II study. Cancer. 1993;72(7):2124-2133.
28. Onkendi EO, Boostrom SY, Sarr MG, et al. Neoadjuvant treatment of duodenal adenocarcinoma: a rescue strategy. J Gastrointest Surg. 2012;16(2):320-324.
29. Markowitz SD, Bertagnolli MM. Molecular basis of colorectal cancer. N Engl J Med. 2009;361(25):2449-2460.
30. Kim GP, Colangelo LH, Wieand HS, et al. Prognostic and predictive roles of high-degree microsatellite instability in colon cancer: a National Cancer Institute–National Surgical Adjuvant Breast and Bowel Project Collaborative Study. J Clin Oncol. 2007;25(7):767-772.
31. Ribic CM, Sargent DJ, Moore MJ, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. N Engl J Med. 2003;349(3):247-257.
32. Sargent DJ, Marsoni S, Monges G, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol. 2010;28(20)-3226.
33. Kim JE, Hong YS, et al. Defective mismatch repair status was not associated with DFS and OS in stage II colon cancer treated with adjuvant chemotherapy. Ann Surg Oncol. 2015;22(3):S630-S637.
34. Benson AB, Venook AP, Al-Hawary MM, et al. Colon cancer, version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2021;19(3):329-359.
35. Overman MJ, Hu C-Y, Kopetz S, et al. A population-based comparison of adenocarcinoma of the large and small intestine: insights into a rare disease. Ann Surg Oncol. 2012;19(5):1439-1445.
36. Compton CC, Fielding LP, Burgart LJ, et al. Prognostic factors in colorectal cancer: College of American Pathologists consensus statement 1999. Arch Pathol Lab Med. 2000;124(7):979-994.
37. Fujita S, Shimoda T, Yoshimura K, et al. Prospective evaluation of prognostic factors in patients with colorectal cancer undergoing curative resection. J Surg Oncol. 2003;84(3):127-131.
38. Liebig C, Ayala G, Wilks J, et al. Perineural invasion is an independent predictor of outcome in colorectal cancer. J Clin Oncol. 2009;27(31):5131-5137.
39. Shah MH, Goldner WS, Benson AB, et al. Neuroendocrine and Adrenal Tumors, Version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2021;19(7):839-868.
40. Aparicio T, Zaanan A, Svrcek M, et al. Small bowel adenocarcinoma: epidemiology, risk factors, diagnosis and treatment. Dig Liver Dis. 2014;46(2):97-104.
41. Halfdanarson TR, McWilliams RR, Donohue JH, et al. A single-institution experience with 491 cases of small bowel adenocarcinoma. Am J Surg. 2010;199(6):797-803.
42. Fishman PN, Pond GR, Moore MJ, et al. Natural history and chemotherapy effectiveness for advanced adenocarcinoma of the small bowel: a retrospective review of 113 cases. Am J Clin Oncol. 2006;29(3):225-231.
43. Czaykowski P, Hui D. Chemotherapy in small bowel adenocarcinoma: 10-year experience of the British Columbia Cancer Agency. Clin Oncol. 2007;19(2):143-149.
44. Gibson MK, Holcroft CA, Kvols LK, et al. Phase II study of 5-fluorouracil, doxorubicin, and mitomycin C for metastatic small bowel adenocarcinoma. Oncologist. 2005;10(2):132-137.
45. Xiang XJ, Liu YW, Zhang L, et al. A phase II study of modified FOLFOX as first-line chemotherapy in advanced small bowel adenocarcinoma. Anti-cancer Drugs. 2012;23(5):561-566.
46. Horimatsu T, Nakayama N, Moriwaki T, et al. A phase II study of 5-fluorouracil/L-leucovorin/oxaliplatin (mFOLFOX6) in Japanese patients with metastatic or unresectable small bowel adenocarcinoma. Int J Clin Oncol. 2017;22(5):905-912.
47. Overman MJ, Varadhachary GR, Kopetz S, et al. Phase II study of capecitabine and oxaliplatin for advanced adenocarcinoma of the small bowel and ampulla of Vater. J Clin Oncol. 2009;27(16):2598-2603.
48. Zhang L, Wang L-Y, Deng Y-M, Wang F-H, Feng F, Chen Y-C, et al. Efficacy of the FOLFOX/CAPOX regimen for advanced small bowel adenocarcinoma: a three-center study from China. J BUON. 2011;16(4):689-696.
49. McWilliams RR, Foster NR, Mahoney MR, et al. North Central Cancer Treatment Group N0543 (Alliance): A phase 2 trial of pharmacogenetic-based dosing of irinotecan, oxaliplatin, and capecitabine as first-line therapy for patients with advanced small bowel adenocarcinoma. Cancer. 2017;123(18):3494-3501.
50. Overman M, Adam L, Raghav K, et al. Phase II study of nab-paclitaxel in refractory small bowel adenocarcinoma and CpG island methylator phenotype (CIMP)-high colorectal cancer. Ann Oncol. 2018;29(1):139-144.
51. Overman MJ, Kopetz S, Wen S, et al. Chemotherapy with 5-fluorouracil and a platinum compound improves outcomes in metastatic small bowel adenocarcinoma. Cancer. 2008;113(8):2038-2045.
52. Zaanan A, Costes L, Gauthier M, et al. Chemotherapy

of advanced small-bowel adenocarcinoma: a multicenter AGEO study. Ann Oncol. 2010;21(9):1786-1793.
53. Tsushima T, Taguri M, Honma Y, et al. Multicenter retrospective study of 132 patients with unresectable small bowel adenocarcinoma treated with chemotherapy. Oncologist. 2012;17(9):1163-1170.
54. Zaanan A, Gauthier M, Malka D, et al. Second-line chemotherapy with fluorouracil, leucovorin, and irinotecan (FOLFIRI regimen) in patients with advanced small bowel adenocarcinoma after failure of first-line platinum-based chemotherapy: a multicenter AGEO study. Cancer. 2011;117(7):1422-1428.
55. Schrock AB, Devoe CE, McWilliams R, et al. Genomic profiling of small-bowel adenocarcinoma. JAMA Oncol. 2017;3(11):1546-1553.
56. Hänninen UA, Katainen R, Tanskanen T, et al. Exome-wide somatic mutation characterization of small bowel adenocarcinoma. PLoS Genet. 2018;14(3):e1007200.
57. Santini D, Fratto M, Spoto C, et al. Cetuximab in small bowel adenocarcinoma: a new friend? Br J Cancer. 2010;103(8):1305.
58. Falcone R, Roberto M, Filetti M, et al. Anti epidermal growth factor receptor therapy in small bowel adenocarcinoma: case report and literature review. Medicine. 2018;97(3):e9672.
59. Gulhati P, Raghav K, Shroff RT, et al. Bevacizumab combined with capecitabine and oxaliplatin in patients with advanced adenocarcinoma of the small bowel or ampulla of vater: A single-center, open-label, phase 2 study. Cancer. 2017;123(6):1011-1017.
60. Overman MJ, Wolff RA, Wang H. Reply: Cetuximab in small bowel adenocarcinoma: a new friend? Br. 2010;103(8):1306.
61. Gulhati P, Raghav K, Shroff R, et al. Phase II study of panitumumab in RAS wild-type metastatic adenocarcinoma of small bowel or ampulla of vater. Oncologist. 2018;23(3):277-e26.
62. Adam L, San Lucas FA, Fowler R, et al. DNA sequencing of small bowel adenocarcinomas identifies targetable recurrent mutations in the ERBB2 signaling pathway. Clin Cancer Res. 2019;25(2):641-651.
63. Pedersen KS, Foster NR, Overman MJ, et al. ZEBRA: A Multicenter Phase II Study of Pembrolizumab in Patients with Advanced Small-Bowel Adenocarcinoma. Clin Cancer Res. 2021;27(13):3641-3648.
64. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017;357(6349):409-413.
65. S, Zhang L, Nafa K, et al. Reliable pan-cancer microsatellite instability assessment by using targeted next-generation sequencing data. JCO Precis Oncol. 2017;1:1-17.
66. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair–deficient cancer: Results from the phase II KEYNOTE-158 study. J Clin Oncol. 2020;38(1):1-10.
67. Latham A, Srinivasan P, Kemel Y, et al. Microsatellite instability is associated with the presence of Lynch syndrome pan-cancer. J Clin Oncol. 2019;37(4):286-295.
68. Parikh AR, He Y, Hong TS, et al. Analysis of DNA damage response gene alterations and tumor mutational burden across 17,486 tubular gastrointestinal carcinomas: implications for therapy. Oncologist. 2019;24(10):1340-1347.