BÖLÜM 34

MİDENİN MALİGN TÜMÖRLERİ

Özgür DEĞER [1] - Hatice Çilem SOLAK [2]

DOI: 10.37609/akya.3785.c247

GİRİŞ

Mide kanserlerinin yaklaşık %90'ı, midenin en yüzeysel tabakasından veya mukozal glandüler yapılardan kaynaklanan adenokarsinomlardır. Bu nedenle, aksi belirtilmediği takdirde, mide kanseri denildiğinde, esas olarak 'adenokarsinom' tanımlanmaktadır. Ancak, mideden kaynaklanan başka kanser türleri de vardır. Bunlar arasında; midenin lenfoid dokusundan kaynaklanan mukoza ilişkili lenfoid doku (MALT) lenfomaları ve mukozayı çevreleyen kaslardan kaynaklanan leiomyosarkomlar bulunur (1).

EPİDEMİYOLOJİ VE RİSK FAKTÖRLERİ

Mide kanseri, küresel olarak en sık görülen beşinci kanser türüdür. Küresel ve ülkeye özgü insidans oranları, Dünya Sağlık Örgütü'nün GLOBOCAN veri tabanında mevcuttur (2). Mide kanseri, dünya çapında kanser ölümlerinde 4. sırada yer almaktadır (3). Mide kanseri, genellikle ileri evrede tanı aldığı için, mortalite oranı yüksektir (4). Ancak, mide kanserine bağlı ölüm oranında dünya genelinde anlamlı bir düşüş olmuştur ve bu durum, bölgeye göre değişmektedir (3, 5).

COĞRAFİ VE GENETİK FAKTÖRLER

Epidemiyolojik çalışmalar, mide kanseri mortalitesinin ırksal ve etnik farklılıklar gösterdiğini ortaya koymaktadır. Amerika Birleşik Devletleri'nde mide kanserinden ölüm oranları Beyaz Amerikalılarda (100.000'de 2,1); Amerikan Yerlisi/Alaska Yerlisi (100.000'de 5,6), Siyahi (100.000'de 5), Hispanik/Latin (100.000'de 4,8) veya Asyalı-Amerikalı/Pasifik Adalı (100.000'de 4,7) olanlara kıyasla, daha düşüktür (6).

Mide kanserinin insidansı, coğrafi bölgelere göre belirgin farklılıklar göstermektedir. En yüksek görülme oranları; Doğu Asya'da (Moğolistan, Çin, Güney Kore ve Japonya), Güney Amerika'nın And dağları yakınlarında ve Doğu Avrupa'da saptanmaktadır (7). En düşük insidans ise; Kuzey Amerika, Kuzey Avrupa, Kuzey Afrika, ve Güneydoğu Asya'daki birçok ülkede görülmektedir (3). Amerika Birleşik Devletleri'nde mide kanseri, 26.000'den fazla hastada saptanmakta ve her yıl yaklaşık 11.000 ölüme neden olmaktadır (6). Mide kanserinin insidansı, düşük ve orta gelirli ülkelerde daha yüksektir (8).

Dünya genelinde, mide kanserinin küresel insidansında, son birkaç dekadda azalma saptanmıştır

[1] Uzm. Dr., İzmir Atatürk Eğitim ve Araştırma Hastanesi, Gastroenteroloji Kliniği, Gastroenteroloji Yandal Asistanı, latrodects@gmail.com, ORCID iD: 0009-0003-9131-4354

[2] Uzm. Dr., Sağlık Bilimleri Üniversitesi, İzmir Tepecik Eğitim ve Araştırma Hastanesi, Gastroenteroloji Kliniği, cilembinicier@yahoo.com.tr, ORCID iD: 00000-0002-3245-2939

KAYNAKLAR

1. Karimi P, Islami F, Anandasabapathy S, et al. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. *Cancer Epidemiol Biomarkers Prev.* 2014;23(5):700-13.
2. Global Cancer Observatory. International Agency for Research on Cancer. W*orld Health Organization* 2023 (Available from: https://gco.iarc.fr/
3. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2024;74(3):229-63.
4. Soerjomataram I, Cabasag C, Bardot A, et al. Cancer survival in Africa, central and south America, and Asia (SURVCAN-3): a population-based benchmarking study in 32 countries. *Lancet Oncol.* 2023;24(1):22-32.
5. Bertuccio P, Chatenoud L, Levi F, et al. Recent patterns in gastric cancer: a global overview. *Int J Cancer.* 2009;125(3):666-73.
6. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024;74(1):12-49.
7. He Y, Wang Y, Luan F, et al. Chinese and global burdens of gastric cancer from 1990 to 2019. *Cancer Med.* 2021;10(10):3461-73.
8. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin.* 2021;71(3):209-49.
9. Haenszel W. Variation in incidence of and mortality from stomach cancer, with particular reference to the United States. *J Natl Cancer Inst.* 1958;21(2):213-62.
10. Coggon D, Barker DJ, Cole RB, et al. Stomach cancer and food storage. J Natl Cancer Inst. 1989;81(15):1178-82.
11. La Vecchia C, Negri E, D'Avanzo B, et al. Electric refrigerator use and gastric cancer risk. *Br J Cancer.* 1990;62(1):136-7.
12. Fitzsimmons D, Osmond C, George S, et al. Trends in stomach and pancreatic cancer incidence and mortality in England and Wales, 1951-2000. *Br J Surg.* 2007;94(9):1162-71.
13. Haenszel W, Kurihara M. Studies of Japanese migrants. I. Mortality from cancer and other diseases among Japanese in the United States. *J Natl Cancer Inst.* 1968;40(1):43-68.
14. Haenszel W, Kurihara M, Segi M, et al. Stomach cancer among Japanese in Hawaii. *J Natl Cancer Inst.* 1972;49(4):969-88.
15. Ikeda Y, Mori M, Kamakura T, et al. Improvements in diagnosis have changed the incidence of histological types in advanced gastric cancer. *Br J Cancer.* 1995;72(2):424-6.
16. Powell J, McConkey CC. Increasing incidence of adenocarcinoma of the gastric cardia and adjacent sites. *Br J Cancer.* 1990;62(3):440-3.
17. Kalish RJ, Clancy PE, Orringer MB, et al. Clinical, epidemiologic, and morphologic comparison between adenocarcinomas arising in Barrett's esophageal mucosa and in the gastric cardia. *Gastroenterology.* 1984;86(3):461-7.
18. *Cancer incidence in five continents. Volume IX*. IARC Sci Publ. 2008(160):1-837.
19. Koea JB, Karpeh MS, Brennan MF. Gastric cancer in young patients: demographic, clinicopathological, and prognostic factors in 92 patients. *Ann Surg Oncol.* 2000;7(5):346-51.
20. Kokkola A, Sipponen P. Gastric carcinoma in young adults. *Hepatogastroenterology.* 2001;48(42):1552-5.
21. Moreira H, Pinto-de-Sousa J, Carneiro F, et al. Early onset gastric cancer no longer presents as an advanced disease with ominous prognosis. *Dig Surg.* 2009;26(3):215-21.
22. Schistosomes, liver flukes and Helicobacter pylori. *IARC Monogr Eval Carcinog Risks Hum.* 1994;61:1-241.
23. Wroblewski LE, Peek RM, Jr., Wilson KT. Helicobacter pylori and gastric cancer: factors that modulate disease risk. *Clin Microbiol Rev.* 2010;23(4):713-39.
24. Pimentel-Nunes P, Libanio D, Marcos-Pinto R, et al. Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa de Endoscopia Digestiva (SPED) guideline update 2019. *Endoscopy.* 2019;51(4):365-88.
25. Ansari S, Yamaoka Y. Helicobacter pylori BabA in adaptation for gastric colonization. *World J Gastroenterol.* 2017;23(23):4158-69.
26. Piscione M, Mazzone M, Di Marcantonio MC, et al. Eradication of Helicobacter pylori and Gastric Cancer: A Controversial Relationship. *Front Microbiol.* 2021;12:630852.
27. Fabian MR, Sonenberg N. The mechanics of miRNA-mediated gene silencing: a look under the hood of miRISC. *Nat Struct Mol Biol.* 2012;19(6):586-93.
28. Pagliari M, Munari F, Toffoletto M, et al. Helicobacter pylori Affects the Antigen Presentation Activity of Macrophages Modulating the Expression of the Immune Receptor CD300E through miR-4270. Front Immunol. 2017;8:1288.
29. Hinshaw DC, Shevde LA. The Tumor Microenvironment Innately Modulates Cancer Progression. *Cancer Res.* 2019;79(18):4557-66.
30. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet.* 2001;357(9255):539-45.
31. Deng R, Zheng H, Cai H, et al. Effects of helicobacter pylori on tumor microenvironment and immunotherapy responses. *Front Immunol.* 2022;13:923477.
32. Gambardella V, Castillo J, Tarazona N, et al. The role of tumor-associated macrophages in gastric cancer development and their potential as a therapeutic target. *Cancer Treat Rev.* 2020;86:102015.
33. Hardbower DM, Asim M, Murray-Stewart T, et al. Arginase 2 deletion leads to enhanced M1 macrophage activation and upregulated polyamine metabolism in response to Helicobacter pylori infection. *Amino Acids.* 2016;48(10):2375-88.
34. Lewis ND, Asim M, Barry DP, et al. Immune evasion by Helicobacter pylori is mediated by induction of macrophage arginase II. *J Immunol.* 2011;186(6):3632-41.
35. Wilson KT, Crabtree JE. Immunology of Helicobacter pylori: insights into the failure of the immune response and perspectives on vaccine studies. *Gastroenterology.* 2007;133(1):288-308.
36. Yamaguchi T, Fushida S, Yamamoto Y, et al. Tumor-associated macrophages of the M2 phenotype contribute to

progression in gastric cancer with peritoneal dissemination. *Gastric Cancer.* 2016;19(4):1052-65.
37. Zhang H, Wang X, Shen Z, et al. Infiltration of diametrically polarized macrophages predicts overall survival of patients with gastric cancer after surgical resection. *Gastric Cancer.* 2015;18(4):740-50.
38. Zhang P, Yang M, Zhang Y, et al. Dissecting the Single-Cell Transcriptome Network Underlying Gastric Premalignant Lesions and Early Gastric Cancer. *Cell Rep.* 2019;27(6):1934-47 e5.
39. Yarden Y, Pines G. The ERBB network: at last, cancer therapy meets systems biology. *Nat Rev Cancer.* 2012;12(8):553-63.
40. Hojo M, Asahara T, Nagahara A, et al. Gut Microbiota Composition Before and After Use of Proton Pump Inhibitors. *Dig Dis Sci.* 2018;63(11):2940-9.
41. Jackson MA, Goodrich JK, Maxan ME, et al. Proton pump inhibitors alter the composition of the gut microbiota. *Gut.* 2016;65(5):749-56.
42. Gao JJ, Zhang Y, Gerhard M, et al. Association Between Gut Microbiota and Helicobacter pylori-Related Gastric Lesions in a High-Risk Population of Gastric Cancer. *Front Cell Infect Microbiol.* 2018;8:202.
43. Coker OO, Dai Z, Nie Y, et al. Mucosal microbiome dysbiosis in gastric carcinogenesis. *Gut.* 2018;67(6):1024-32.
44. Ferreira RM, Pereira-Marques J, Pinto-Ribeiro I, et al. Gastric microbial community profiling reveals a dysbiotic cancer-associated microbiota. *Gut.* 2018;67(2):226-36.
45. Gunathilake MN, Lee J, Choi IJ, et al. Association between the relative abundance of gastric microbiota and the risk of gastric cancer: a case-control study. *Sci Rep.* 2019;9(1):13589.
46. Gotteland M, Brunser O, Cruchet S. Systematic review: are probiotics useful in controlling gastric colonization by Helicobacter pylori? *Aliment Pharmacol Ther.* 2006;23(8):1077-86.
47. Aiba Y, Suzuki N, Kabir AM, et al. Lactic acid-mediated suppression of Helicobacter pylori by the oral administration of Lactobacillus salivarius as a probiotic in a gnotobiotic murine model. *Am J Gastroenterol.* 1998;93(11):2097-101.
48. Bakhti SZ, Latifi-Navid S. Oral microbiota and Helicobacter pylori in gastric carcinogenesis: what do we know and where next? *BMC Microbiol.* 2021;21(1):71.
49. Cao Y, Wang D, Mo G, et al. Gastric precancerous lesions:occurrence, development factors, and treatment. *Front Oncol.* 2023;13:1226652.
50. Loh JT, Shaffer CL, Piazuelo MB, et al. Analysis of cagA in Helicobacter pylori strains from Colombian populations with contrasting gastric cancer risk reveals a biomarker for disease severity. *Cancer Epidemiol Biomarkers Prev.* 2011;20(10):2237-49.
51. Lauren P. The Two Histological Main Types of Gastric Carcinoma: Diffuse and So-Called Intestinal-Type Carcinoma. An Attempt at a Histo-Clinical Classification. *Acta Pathol Microbiol Scand.* 1965;64:31-49.
52. Diet, nutrition, and the prevention of chronic diseases. Report of a WHO Study Group. *World Health Organ Tech Rep Ser.* 1990;797:1-204.
53. Joossens JV, Hill MJ, Elliott P, et al. Dietary salt, nitrate and stomach cancer mortality in 24 countries. European Cancer Prevention (ECP) and the INTERSALT Cooperative Research Group. *Int J Epidemiol.* 1996;25(3):494-504.
54. Kono S, Hirohata T. Nutrition and stomach cancer. Cancer Causes Control. 1996;7(1):41-55.
55. Kronsteiner-Gicevic S, Thompson AS, Gaggl M, et al. Adding salt to food at table as an indicator of gastric cancer risk among adults: a prospective study. *Gastric Cancer.* 2024;27(4):714-21.
56. Peleteiro B, Lopes C, Figueiredo C, et al. Salt intake and gastric cancer risk according to Helicobacter pylori infection, smoking, tumour site and histological type. *Br J Cancer.* 2011;104(1):198-207.
57. Shikata K, Kiyohara Y, Kubo M, et al. A prospective study of dietary salt intake and gastric cancer incidence in a defined Japanese population: the Hisayama study. *Int J Cancer.* 2006;119(1):196-201.
58. Tsugane S, Sasazuki S. Diet and the risk of gastric cancer: review of epidemiological evidence. *Gastric Cancer.* 2007;10(2):75-83.
59. Collatuzzo G, Pelucchi C, Negri E, et al. Exploring the interactions between Helicobacter pylori (Hp) infection and other risk factors of gastric cancer: A pooled analysis in the Stomach cancer Pooling (StoP) Project. *Int J Cancer.* 2021;149(6):1228-38.
60. Tricker AR. N-nitroso compounds and man: sources of exposure, endogenous formation and occurrence in body fluids. *Eur J Cancer Prev.* 1997;6(3):226-68.
61. You WC, Zhang L, Yang CS, et al. Nitrite, N-nitroso compounds, and other analytes in physiological fluids in relation to precancerous gastric lesions. *Cancer Epidemiol Biomarkers Prev.* 1996;5(1):47-52.
62. Jakszyn P, Bingham S, Pera G, et al. Endogenous versus exogenous exposure to N-nitroso compounds and gastric cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST) study. *Carcinogenesis.* 2006;27(7):1497-501.
63. Bouvard V, Loomis D, Guyton KZ, et al., International Agency for Research on Cancer Monograph Working G. Carcinogenicity of consumption of red and processed meat. *Lancet Oncol.* 2015;16(16):1599-600.
64. Lauby-Secretan B, Scoccianti C, Loomis D, et al., International Agency for Research on Cancer Handbook Working G. Body Fatness and Cancer--Viewpoint of the IARC Working Group. *N Engl J Med.* 2016;375(8):794-8.
65. Yang P, Zhou Y, Chen B, et al. Overweight, obesity and gastric cancer risk: results from a meta-analysis of cohort studies. *Eur J Cancer.* 2009;45(16):2867-73.
66. Ladeiras-Lopes R, Pereira AK, Nogueira A, et al. Smoking and gastric cancer: systematic review and meta-analysis of cohort studies. *Cancer Causes Control.* 2008;19(7):689-701.
67. Gonzalez CA, Pera G, Agudo A, et al. Smoking and the risk of gastric cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). *Int J Cancer.* 2003;107(4):629-34.
68. Machlowska J, Baj J, Sitarz M, et al. Gastric Cancer: Epidemiology, Risk Factors, Classification, Genomic Characteristics and Treatment Strategies. *Int J Mol Sci.* 2020;21(11).
69. Pang D, Burges DC, Sorahan T. Mortality study of nickel platers with special reference to cancers of the stomach

and lung, 1945-93. *Occup Environ Med.* 1996;53(10):714-7.
70. Raj A, Mayberry JF, Podas T. Occupation and gastric cancer. *Postgrad Med J.* 2003;79(931):252-8.
71. Boysen T, Mohammadi M, Melbye M, et al. EBV-associated gastric carcinoma in high- and low-incidence areas for nasopharyngeal carcinoma. *Br J Cancer.* 2009;101(3):530-3.
72. Takada K. Epstein-Barr virus and gastric carcinoma. *Mol Pathol.* 2000;53(5):255-61.
73. Chang MS, Uozaki H, Chong JM, et al. CpG island methylation status in gastric carcinoma with and without infection of Epstein-Barr virus. *Clin Cancer Res.* 2006;12(10):2995-3002.
74. Fukayama M. Epstein-Barr virus and gastric carcinoma. *Pathol Int.* 2010;60(5):337-50.
75. Zhao J, Jin H, Cheung KF, et al. Zinc finger E-box binding factor 1 plays a central role in regulating Epstein-Barr virus (EBV) latent-lytic switch and acts as a therapeutic target in EBV-associated gastric cancer. *Cancer.* 2012;118(4):924-36.
76. Fukayama M, Chong JM, Uozaki H. Pathology and molecular pathology of Epstein-Barr virus-associated gastric carcinoma. *Curr Top Microbiol Immunol.* 2001;258:91-102.
77. Kusano M, Toyota M, Suzuki H, et al. Genetic, epigenetic, and clinicopathologic features of gastric carcinomas with the CpG island methylator phenotype and an association with Epstein-Barr virus. *Cancer.* 2006;106(7):1467-79.
78. Lee JH, Kim SH, Han SH, et al. Clinicopathological and molecular characteristics of Epstein-Barr virus-associated gastric carcinoma: a meta-analysis. *J Gastroenterol Hepatol.* 2009;24(3):354-65.
79. Murphy G, Pfeiffer R, Camargo MC, et al. Meta-analysis shows that prevalence of Epstein-Barr virus-positive gastric cancer differs based on sex and anatomic location. *Gastroenterology.* 2009;137(3):824-33.
80. van Beek J, zur Hausen A, Klein Kranenbarg E, et al. EBV-positive gastric adenocarcinomas: a distinct clinicopathologic entity with a low frequency of lymph node involvement. *J Clin Oncol.* 2004;22(4):664-70.
81. Barker DJ, Coggon D, Osmond C, et al. Poor housing in childhood and high rates of stomach cancer in England and Wales. *Br J Cancer.* 1990;61(4):575-8.
82. Komatsu S, Ichikawa D, Okamoto K, et al. Progression of remnant gastric cancer is associated with duration of follow-up following distal gastrectomy. *World J Gastroenterol.* 2012;18(22):2832-6.
83. Takeno S, Hashimoto T, Maki K, et al. Gastric cancer arising from the remnant stomach after distal gastrectomy: a review. World J Gastroenterol. 2014;20(38):13734-40.
84. Tersmette AC, Offerhaus GJ, Tersmette KW, et al. Meta-analysis of the risk of gastric stump cancer: detection of high risk patient subsets for stomach cancer after remote partial gastrectomy for benign conditions. *Cancer Res.* 1990;50(20):6486-9.
85. Henderson TO, Oeffinger KC, Whitton J, et al. Secondary gastrointestinal cancer in childhood cancer survivors: a cohort study. *Ann Intern Med.* 2012;156(11):757-66, W-260.
86. Morton LM, Dores GM, Curtis RE, et al. Stomach cancer risk after treatment for hodgkin lymphoma. *J Clin Oncol.* 2013;31(27):3369-77.
87. Ferro A, Costa AR, Morais S, et al. Fruits and vegetables intake and gastric cancer risk: A pooled analysis within the Stomach cancer Pooling Project. *Int J Cancer.* 2020;147(11):3090-101.
88. Larsson SC, Bergkvist L, Wolk A. Fruit and vegetable consumption and incidence of gastric cancer: a prospective study. *Cancer Epidemiol Biomarkers Prev.* 2006;15(10):1998-2001.
89. Lunet N, Valbuena C, Vieira AL, et al. Fruit and vegetable consumption and gastric cancer by location and histological type: case-control and meta-analysis. *Eur J Cancer Prev.* 2007;16(4):312-27.
90. La Vecchia C, Negri E, Decarli A, et al. A case-control study of diet and gastric cancer in northern Italy. *Int J Cancer.* 1987;40(4):484-9.
91. Wang Q, Chen Y, Wang X, et al. Consumption of fruit, but not vegetables, may reduce risk of gastric cancer: results from a meta-analysis of cohort studies. *Eur J Cancer.* 2014;50(8):1498-509.
92. Bai X, Li X, Ding S, et al. Adherence to the Mediterranean Diet and Risk of Gastric Cancer: A Systematic Review and Meta-Analysis. *Nutrients.* 2023;15(17).
93. Duell EJ, Travier N, Lujan-Barroso L, et al. Menstrual and reproductive factors, exogenous hormone use, and gastric cancer risk in a cohort of women from the European Prospective Investigation Into Cancer and Nutrition. *Am J Epidemiol.* 2010;172(12):1384-93.
94. Freedman ND, Chow WH, Gao YT, et al. Menstrual and reproductive factors and gastric cancer risk in a large prospective study of women. *Gut.* 2007;56(12):1671-7.
95. Wang Z, Butler LM, Wu AH, et al. Reproductive factors, hormone use and gastric cancer risk: The Singapore Chinese Health Study. *Int J Cancer.* 2016;138(12):2837-45.
96. Capparelli R, Iannelli D. Epigenetics and Helicobacter pylori. *Int J Mol Sci.* 2022;23(3).
97. Kumar S, Patel GK, Ghoshal UC. Helicobacter pylori-Induced Inflammation: Possible Factors Modulating the Risk of Gastric Cancer. *Pathogens.* 2021;10(9).
98. Lu Y, Liu H, Yang K, et al. A comprehensive update: gastrointestinal microflora, gastric cancer and gastric premalignant condition, and intervention by traditional Chinese medicine. *J Zhejiang Univ Sci B.* 2022;23(1):1-18.
99. Correa P. Human gastric carcinogenesis: a multistep and multifactorial process--First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res.* 1992;52(24):6735-40.
100. Kapadia CR. Gastric atrophy, metaplasia, and dysplasia: a clinical perspective. *J Clin Gastroenterol. 2*003;36(5 Suppl):S29-36; discussion S61-2.
101. Correa P. A human model of gastric carcinogenesis. *Cancer Res.* 1988;48(13):3554-60.
102. Genta RM. Acid suppression and gastric atrophy: sifting fact from fiction. *Gut.* 1998;43 Suppl 1(Suppl 1):S35-8.
103. Sobala GM, O'Connor HJ, Dewar EP, et al. Bile reflux and intestinal metaplasia in gastric mucosa. *J Clin Pathol.* 1993;46(3):235-40.
104. Watanabe H. Experimentally induced intestinal metaplasia in Wistar rats by X-ray irradiation. *Gastroenterology.* 1978;75(5):796-9.

105. Correa P, Cuello C, Duque E. Carcinoma and intestinal metaplasia of the stomach in Colombian migrants. *J Natl Cancer Inst.* 1970;44(2):297-306.
106. Sasajima K, Kawachi T, Matsukura N, et al. Intestinal metaplasia and adenocarcinoma induced in the stomach of rats by N-propyl-N'-nitro-N-nitrosoguanidine. *J Cancer Res Clin Oncol.* 1979;94(2):201-6.
107. Shimoyama T, Fukuda S, Tanaka M, et al. Evaluation of the applicability of the gastric carcinoma risk index for intestinal type cancer in Japanese patients infected with Helicobacter pylori. *Virchows Arch.* 2000;436(6):585-7.
108. Piazuelo MB, Camargo MC, Mera RM, et al. Eosinophils and mast cells in chronic gastritis: possible implications in carcinogenesis. *Hum Pathol.* 2008;39(9):1360-9.
109. Rugge M, Farinati F, Baffa R, et al. Gastric epithelial dysplasia in the natural history of gastric cancer: a multicenter prospective follow-up study. Interdisciplinary Group on Gastric Epithelial Dysplasia. *Gastroenterology.* 1994;107(5):1288-96.
110. Smyth EC, Nilsson M, Grabsch HI, et al. European Chapter of International Gastric Cancer, Association. *Gastric cancer. Lancet.* 2020;396(10251):635-48.
111. van der Post RS, Vogelaar IP, Carneiro F, et al. Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. *J Med Genet.* 2015;52(6):361-74.
112. Stjepanovic N, Moreira L, Carneiro F, et al. Esmo Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Hereditary gastrointestinal cancers: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-updagger. *Ann Oncol.* 2019;30(10):1558-71.
113. Nakamura K, Sugano H, Takagi K. Carcinoma of the stomach in incipient phase: its histogenesis and histological appearances. *Gan.* 1968;59(3):251-8.
114. WHO. Digestive System Tumours, WHO Classification of Tumours Series. *International Agency for Research on Cancer Lyon,* France; 2019.
115. Gotoda T, Jung HY. Endoscopic resection (endoscopic mucosal resection/ endoscopic submucosal dissection) for early gastric cancer. *Dig Endosc.* 2013;25 Suppl 1:55-63.
116. Mariette C, Carneiro F, Grabsch HI, et al. European Chapter of International Gastric Cancer, Association. Correction to: Consensus on the pathological definition and classification of poorly cohesive gastric carcinoma. *Gastric Cancer.* 2019;22(2):421.
117. Lei Z, Tan IB, Das K, et al. Identification of molecular subtypes of gastric cancer with different responses to PI3-kinase inhibitors and 5-fluorouracil. *Gastroenterology.* 2013;145(3):554-65.
118. Tan IB, Ivanova T, Lim KH, et al. Intrinsic subtypes of gastric cancer, based on gene expression pattern, predict survival and respond differently to chemotherapy. *Gastroenterology.* 2011;141(2):476-85, 85 e1-11.
119. Cancer Genome Atlas Research N. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature.* 2014;513(7517):202-9.
120. Cristescu R, Lee J, Nebozhyn M, et al. Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. *Nat Med.* 2015;21(5):449-56.
121. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet.* 2010;376(9742):687-97.
122. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet.* 2021;398(10294):27-40.
123. Kulangara K, Zhang N, Corigliano E, et al. Clinical Utility of the Combined Positive Score for Programmed Death Ligand-1 Expression and the Approval of Pembrolizumab for Treatment of Gastric Cancer. *Arch Pathol Lab Med.* 2019;143(3):330-7.
124. Wainberg ZA, Fuchs CS, Tabernero J, et al. Efficacy of Pembrolizumab Monotherapy for Advanced Gastric/Gastroesophageal Junction Cancer with Programmed Death Ligand 1 Combined Positive Score ≥10. *Clin Cancer Res.* 2021;27(7):1923-31.
125. Pietrantonio F, Miceli R, Raimondi A, et al. Individual Patient Data Meta-Analysis of the Value of Microsatellite Instability As a Biomarker in Gastric Cancer. *J Clin Oncol.* 2019;37(35):3392-400.
126. Lordick F. Chemotherapy for resectable microsatellite instability-high gastric cancer? *Lancet Oncol.* 2020;21(2):203.
127. Smyth EC. Chemotherapy for resectable microsatellite instability-high gastric cancer? *Lancet Oncol.* 2020;21(2):204.
128. Chao J, Fuchs CS, Shitara K, et al. Assessment of Pembrolizumab Therapy for the Treatment of Microsatellite Instability-High Gastric or Gastroesophageal Junction Cancer Among Patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 Clinical Trials. *JAMA Oncol.* 2021;7(6):895-902.
129. Smyth EC, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. *Lancet.* 2020;396(10251):635-48.
130. Lordick F, Carneiro F, Cascinu S, et al. Esmo Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol.* 2022;33(10):1005-20.
131. Gravalos C, Jimeno A. HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. *Ann Oncol.* 2008;19(9):1523-9.
132. Wang HB, Liao XF, Zhang J. Clinicopathological factors associated with HER2-positive gastric cancer: A meta-analysis. *Medicine (Baltimore).* 2017;96(44):e8437.
133. Busuttil RA, Zapparoli GV, Haupt S, et al. Role of p53 in the progression of gastric cancer. *Oncotarget.* 2014;5(23):12016-26.
134. Xing X, Guo J, Ding G, et al. Analysis of PD1, PDL1, PDL2 expression and T cells infiltration in 1014 gastric cancer patients. *Oncoimmunology.* 2018;7(3):e1356144.
135. Pilozzi E, Talerico C, Platt A, et al. p73 gene mutations in gastric adenocarcinomas. *Mol Pathol.* 2003;56(1):60-2.
136. Wang L, Zhang XY, Xu L, et al. Expression and significance of p53 and mdm2 in atypical intestinal metaplasia and gastric carcinoma. *Oncol Lett.* 2011;2(4):707-12.

137. Wu J, Liu X, Cai H, et al. Prediction of tumor recurrence after curative resection in gastric carcinoma based on bcl-2 expression. *World J Surg Oncol.* 2014;12:40.
138. Gao P, Zhou GY, Liu Y, et al. Alteration of cyclin D1 in gastric carcinoma and its clinicopathologic significance. *World J Gastroenterol.* 2004;10(20):2936-9.
139. Arici DS, Tuncer E, Ozer H, et al. Expression of retinoblastoma and cyclin D1 in gastric carcinoma. *Neoplasma.* 2009;56(1):63-7.
140. Hayashi K, Metzger R, Salonga D, et al. High frequency of simultaneous loss of p16 and p16beta gene expression in squamous cell carcinoma of the esophagus but not in adenocarcinoma of the esophagus or stomach. *Oncogene.* 1997;15(12):1481-8.
141. Boltin D, Niv Y. Mucins in Gastric Cancer - An Update. *J Gastrointest Dig Syst.* 2013;3(123):15519.
142. Lee HS, Lee HK, Kim HS, et al. MUC1, MUC2, MUC5AC, and MUC6 expressions in gastric carcinomas: their roles as prognostic indicators. *Cancer.* 2001;92(6):1427-34.
143. Sandusky GE, Mintze KS, Pratt SE, et al. Expression of multidrug resistance-associated protein 2 (MRP2) in normal human tissues and carcinomas using tissue microarrays. *Histopathology.* 2002;41(1):65-74.
144. Qiao W, Wang T, Zhang L, et al. Association between single genetic polymorphisms of MDR1 gene and gastric cancer susceptibility in Chinese. *Med Oncol.* 2013;30(3):643.
145. Zhu CY, Lv YP, Yan DF, et al. Knockdown of MDR1 increases the sensitivity to adriamycin in drug resistant gastric cancer cells. *Asian Pac J Cancer Prev. 2*013;14(11):6757-60.
146. Hayes PC, Bouchier IA, Beckett GJ. Glutathione S-transferase in humans in health and disease. *Gut.* 1991;32(7):813-8.
147. Yu P, Du Y, Cheng X, et al. Expression of multidrug resistance-associated proteins and their relation to postoperative individualized chemotherapy in gastric cancer. *World J Surg Oncol.* 2014;12:307.
148. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature.* 2014;513(7517):202-9.
149. Polom K, Marrelli D, Smyth EC, et al. The Role of Microsatellite Instability in Positive Margin Gastric Cancer Patients. *Surg Innov.* 2018;25(2):99-104.
150. Ballehaninna UK, Chamberlain RS. The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: An evidence based appraisal. *J Gastrointest Oncol.* 2012;3(2):105-19.
151. Feng F, Tian Y, Xu G, et al. Diagnostic and prognostic value of CEA, CA19-9, AFP and CA125 for early gastric cancer. BMC Cancer. 2017;17(1):737.
152. Kochi M, Fujii M, Kanamori N, et al. Evaluation of serum CEA and CA19-9 levels as prognostic factors in patients with gastric cancer. *Gastric Cancer.* 2000;3(4):177-86.
153. Sisik A, Kaya M, Bas G, et al. CEA and CA 19-9 are still valuable markers for the prognosis of colorectal and gastric cancer patients. *Asian Pac J Cancer Prev.* 2013;14(7):4289-94.
154. Zhou YC, Zhao HJ, Shen LZ. Preoperative serum CEA and CA19-9 in gastric cancer--a single tertiary hospital study of 1,075 cases. *Asian Pac J Cancer Prev.* 2015;16(7):2685-91.
155. Chen C, Chen Q, Zhao Q, et al. Value of Combined Detection of Serum CEA, CA72-4, CA19-9, CA15-3 and CA12-5 in the Diagnosis of Gastric Cancer. *Ann Clin Lab Sci.* 2017;47(3):260-3.
156. Sawayama H, Iwatsuki M, Kuroda D, et al. The association of the lymph node ratio and serum carbohydrate antigen 19-9 with early recurrence after curative gastrectomy for gastric cancer. *Surg Today.* 2018;48(11):994-1003.
157. Hasbahceci M, Malya FU, Kunduz E, et al. Use of serum and peritoneal CEA and CA19-9 in prediction of peritoneal dissemination and survival of gastric adenocarcinoma patients: are they prognostic factors? *Ann R Coll Surg Engl.* 2018;100(4):257-66.
158. Sun Z, Zhang N. Clinical evaluation of CEA, CA19-9, CA72-4 and CA125 in gastric cancer patients with neoadjuvant chemotherapy. *World J Surg Oncol.* 2014;12:397.
159. Song YX, Huang XZ, Gao P, et al. Clinicopathologic and Prognostic Value of Serum Carbohydrate Antigen 19-9 in Gastric Cancer: A Meta-Analysis. *Dis Markers.* 2015;2015:549843.
160. Yu J, Zheng W. An Alternative Method for Screening Gastric Cancer Based on Serum Levels of CEA, CA19-9, and CA72-4. *J Gastrointest Cancer.* 2018;49(1):57-62.
161. Shen M, Wang H, Wei K, et al. Five common tumor biomarkers and CEA for diagnosing early gastric cancer: A protocol for a network meta-analysis of diagnostic test accuracy. *Medicine (Baltimore).* 2018;97(19):e0577.
162. Coudray N, Ocampo PS, Sakellaropoulos T, et al. Classification and mutation prediction from non-small cell lung cancer histopathology images using deep learning. *Nat Med.* 2018;24(10):1559-67.
163. Kather JN, Pearson AT, Halama N, et al. Deep learning can predict microsatellite instability directly from histology in gastrointestinal cancer. *Nat Med.* 2019;25(7):1054-6.
164. Febbo PG, Martin AM, Scher HI, et al. Minimum Technical Data Elements for Liquid Biopsy Data Submitted to Public Databases. *Clin Pharmacol Ther.* 2020;107(4):730-4.
165. Babayan A, Pantel K. Advances in liquid biopsy approaches for early detection and monitoring of cancer. *Genome Med.* 2018;10(1):21.
166. Leja M, Linē A. Early detection of gastric cancer beyond endoscopy - new methods. *Best Pract Res Clin Gastroenterol.* 2021;50-51:101731.
167. Leal A, van Grieken NCT, Palsgrove DN, et al. White blood cell and cell-free DNA analyses for detection of residual disease in gastric cancer. *Nat Commun.* 2020;11(1):525.
168. Maron SB, Chase LM, Lomnicki S, et al. Circulating Tumor DNA Sequencing Analysis of Gastroesophageal Adenocarcinoma. *Clin Cancer Res.* 2019;25(23):7098-112.
169. Ruschoff J, Hanna W, Bilous M, et al. HER2 testing in gastric cancer: a practical approach. *Mod Pathol.* 2012;25(5):637-50.
170. Li Y, Zhang X, Liu D, et al. Evolutionary Expression of HER2 Conferred by Chromosome Aneuploidy on Circulating Gastric Cancer Cells Contributes to Developing Targeted and Chemotherapeutic Resistance. *Clin Cancer Res.* 2018;24(21):5261-71.
171. Pectasides E, Stachler MD, Derks S, et al. Genomic Heterogeneity as a Barrier to Precision Medicine in Gastroe-

sophageal Adenocarcinoma. *Cancer Discov.* 2018;8(1):37-48.
172. Wang DS, Liu ZX, Lu YX, et al. Liquid biopsies to track trastuzumab resistance in metastatic HER2-positive gastric cancer. *Gut.* 2019;68(7):1152-61.
173. Allum W, Lordick F, Alsina M, et al. ECCO essential requirements for quality cancer care: Oesophageal and gastric cancer. Crit Rev Oncol Hematol. 2018;122:179-93.
174. Morgenstern L. The Virchow-Troisier node: a historical note. *Am J Surg.* 1979;138(5):703.
175. Pieslor PC, Hefter LG. Umbilical metastasis from prostatic carcinoma--Sister Joseph nodule. *Urology.* 1986;27(6):558-9.
176. Kobayashi O, Sugiyama Y, Konishi K, et al. Solitary metastasis to the left axillary lymph node after curative gastrectomy in gastric cancer. *Gastric Cancer.* 2002;5(3):173-6.
177. Gilliland R, Gill PJ. Incidence and prognosis of Krukenberg tumour in Northern Ireland. *Br J Surg.* 1992;79(12):1364-6.
178. Winne BB. Blumer's shelf tumor with primary carcinoma of the lung. A case report. *J Int Coll Surg.* 1965;44(5):477-81.
179. Smyth EC, Verheij M, Allum W, et al. Esmo Guidelines Committee. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2016;27(suppl 5):v38-v49.
180. Edge SB, American Joint Committee on Cancer ACS. AJCC cancer staging handbook: from the AJCC cancer staging manual: Springer; 2010.
181. Mocellin S, Pasquali S. Diagnostic accuracy of endoscopic ultrasonography (EUS) for the preoperative locoregional staging of primary gastric cancer. *Cochrane Database Syst Rev.* 2015;2015(2):CD009944.
182. Smyth E, Schoder H, Strong VE, et al. A prospective evaluation of the utility of 2-deoxy-2-((18) F]fluoro-D-glucose positron emission tomography and computed tomography in staging locally advanced gastric cancer. *Cancer.* 2012;118(22):5481-8.
183. Jamel S, Markar SR, Malietzis G, et al. Prognostic significance of peritoneal lavage cytology in staging gastric cancer: systematic review and meta-analysis. *Gastric Cancer.* 2018;21(1):10-8.
184. Kwee RM, Kwee TC. Imaging in assessing lymph node status in gastric cancer. *Gastric Cancer.* 2009;12(1):6-22.
185. Gertsen EC, Brenkman HJF, van Hillegersberg R, et al. 18F-Fludeoxyglucose-Positron Emission Tomography/Computed Tomography and Laparoscopy for Staging of Locally Advanced Gastric Cancer: A Multicenter Prospective Dutch Cohort Study (PLASTIC). *JAMA Surg.* 2021;156(12):e215340.
186. Leake PA, Cardoso R, Seevaratnam R, et al. A systematic review of the accuracy and indications for diagnostic laparoscopy prior to curative-intent resection of gastric cancer. *Gastric Cancer.* 2012;15 Suppl 1:S38-47.
187. Leake PA, Cardoso R, Seevaratnam R, et al. A systematic review of the accuracy and utility of peritoneal cytology in patients with gastric cancer. *Gastric Cancer.* 2012;15 Suppl 1:S27-37.
188. Japanese Gastric Cancer A. Japanese gastric cancer treatment guidelines 2014 (ver. 4). *Gastric Cancer.* 2017;20(1):1-19.
189. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy.* 2015;47(9):829-54.
190. Davis JL, Ripley RT. Postgastrectomy Syndromes and Nutritional Considerations Following Gastric Surgery. *Surg Clin North Am.* 2017;97(2):277-93.
191. Hiki N, Nunobe S, Kubota T, et al. Function-preserving gastrectomy for early gastric cancer. *Ann Surg Oncol.* 2013;20(8):2683-92.
192. Roberts GP, Kay RG, Howard J, et al. Gastrectomy with Roux-en-Y reconstruction as a lean model of bariatric surgery. *Surg Obes Relat Dis.* 2018;14(5):562-8.
193. Yamamoto H, Mori T, Tsuchihashi H, et al. A possible role of GLP-1 in the pathophysiology of early dumping syndrome. *Dig Dis Sci.* 2005;50(12):2263-7.
194. Kinoshita T, Maruyama ea. Treatment results of gastric cancer patients: Japanese experience. *Gastric cancer: Springer;* 1993. p. 319-30.
195. Wu CW, Hsiung CA, Lo SS, et al. Nodal dissection for patients with gastric cancer: a randomised controlled trial. *Lancet Oncol.* 2006;7(4):309-15.
196. Sasako M, Sano T, Yamamoto S, et al. Japan Clinical Oncology, Group. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *N Engl J Med.* 2008;359(5):453-62.
197. Dikken JL, van Sandick JW, Allum WH, et al. Differences in outcomes of oesophageal and gastric cancer surgery across Europe. *Br J Surg.* 2013;100(1):83-94.
198. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med.* 2008;358(1):36-46.
199. Al-Batran SE, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol.* 2008;26(9):1435-42.
200. Koizumi W, Narahara H, Hara T, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol.* 2008;9(3):215-21.
201. Hall PS, Swinson D, Cairns DA, et al. Efficacy of Reduced-Intensity Chemotherapy With Oxaliplatin and Capecitabine on Quality of Life and Cancer Control Among Older and Frail Patients With Advanced Gastroesophageal Cancer: The GO2 Phase 3 Randomized Clinical Trial. *JAMA Oncol.* 2021;7(6):869-77.
202. Group G, Paoletti X, Oba K, et al. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. *JAMA.* 2010;303(17):1729-37.
203. Cats A, Jansen EPM, van Grieken NCT, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. *Lancet Oncol.* 2018;19(5):616-28.
204. de Steur WO, van Amelsfoort RM, Hartgrink HH, et al. Adjuvant chemotherapy is superior to chemoradiation after D2 surgery for gastric cancer in the per-protocol analysis of the randomized CRITICS trial. *Ann Oncol.* 2021;32(3):360-7.

205. Lee J, Lim DH, Kim S, et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. *J Clin Oncol.* 2012;30(3):268-73.
206. Park SH, Lim DH, Sohn TS, et al. A randomized phase III trial comparing adjuvant single-agent S1, S-1 with oxaliplatin, and postoperative chemoradiation with S-1 and oxaliplatin in patients with node-positive gastric cancer after D2 resection: the ARTIST 2 trial(). *Ann Oncol.* 2021;32(3):368-74.
207. Park SH, Sohn TS, Lee J, et al. Phase III Trial to Compare Adjuvant Chemotherapy With Capecitabine and Cisplatin Versus Concurrent Chemoradiotherapy in Gastric Cancer: Final Report of the Adjuvant Chemoradiotherapy in Stomach Tumors Trial, Including Survival and Subset Analyses. *J Clin Oncol.* 2015;33(28):3130-6.
208. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med.* 2001;345(10):725-30.
209. Mandelker D, Donoghue M, Talukdar S, et al. Erratum to 'Germline-focussed analysis of tumour-only sequencing: recommendations from the ESMO Precision Medicine Working Group': (Annals of Oncology 30 (2019) 1221-1231). *Ann Oncol.* 2021;32(8):1069-71.
210. Andre T, Tougeron ea. Neoadjuvant nivolumab plus ipilimumab and adjuvant nivolumab in patients (pts) with localized microsatellite instability-high (MSI)/mismatch repair deficient (dMMR) oeso-gastric adenocarcinoma (OGA): The GERCOR NEONIPIGA phase II study. American Society of Clinical Oncology; 2022.
211. Bass AJ, Thorsson V, Shmulevich I, Reynolds SM, Miller M, Bernard B, et al. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature.* 2014;513(7517):202-9.
212. Van Cutsem E, Bang YJ, Feng-Yi F, et al. HER2 screening data from ToGA: targeting HER2 in gastric and gastroesophageal junction cancer. *Gastric Cancer.* 2015;18(3):476-84.
213. Shitara K, Van Cutsem E, Bang YJ, et al. Efficacy and Safety of Pembrolizumab or Pembrolizumab Plus Chemotherapy vs Chemotherapy Alone for Patients With First-line, Advanced Gastric Cancer: The KEYNOTE-062 Phase 3 Randomized Clinical Trial. *JAMA Oncol.* 2020;6(10):1571-80.
214. Pietrantonio F, Randon G, Di Bartolomeo M, et al. Predictive role of microsatellite instability for PD-1 blockade in patients with advanced gastric cancer: a meta-analysis of randomized clinical trials. *ESMO Open.* 2021;6(1):100036.
215. Wagner AD, Syn NL, Moehler M, et al. Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev.* 2017;8(8):Cd004064.
216. Hironaka S, Ueda S, Yasui H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. *J Clin Oncol.* 2013;31(35):4438-44.
217. Wilke H, Muro K, Van Cutsem E, Oh SC, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol.* 2014;15(11):1224-35.
218. Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. *N Engl J Med.* 2020;382(25):2419-30.
219. Shitara K, Doi T, Dvorkin M, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2018;19(11):1437-48.
220. Fujitani K, Yang HK, Mizusawa J, et al. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. *Lancet Oncol.* 2016;17(3):309-18.
221. Eveno C, Jouvin I, Pocard M. PIPAC EstoK 01: Pressurized IntraPeritoneal Aerosol Chemotherapy with cisplatin and doxorubicin (PIPAC C/D) in gastric peritoneal metastasis: a randomized and multicenter phase II study. Pleura Peritoneum. 2018;3(2):20180116.
222. Lu Z, Fang Y, Liu C, et al. Early Interdisciplinary Supportive Care in Patients With Previously Untreated Metastatic Esophagogastric Cancer: A Phase III Randomized Controlled Trial. *J Clin Oncol.* 2021;39(7):748-56.
223. Mansoor W, Roeland EJ, Chaudhry A, et al. Early Weight Loss as a Prognostic Factor in Patients with Advanced Gastric Cancer: Analyses from REGARD, RAINBOW, and RAINFALL Phase III Studies. *Oncologist.* 2021;26(9):e1538-e47.
224. Dai Y, Li C, Xie Y, et al. Interventions for dysphagia in oesophageal cancer. *Cochrane Database Syst Rev.* 2014;2014(10):Cd005048.
225. Bergquist H, Wenger U, Johnsson E, et al. Stent insertion or endoluminal brachytherapy as palliation of patients with advanced cancer of the esophagus and gastroesophageal junction. Results of a randomized, controlled clinical trial. *Dis Esophagus.* 2005;18(3):131-9.
226. Kawabata H, Hitomi M, Motoi S. Management of Bleeding from Unresectable Gastric Cancer. *Biomedicines.* 2019;7(3).