BÖLÜM 12

Özofagus Kanserinde Tedavi

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2020 yılında 604 bin yeni tanısı konan ve 544 bin kişinin hayatını kaybetmesine sebep olan özofagus kanseri dünyada en sık görülen 8. kanserdir ve kanserden ölümlerde 6. sıradadır (1). İnsidansı özellikle gelişmekte olan ülkelerde daha yüksek ve erkeklerde kadınlara göre 3-4 kat daha yüksektir (2). En yüksek insidans İran, Orta Asya cumhuriyetleri ve kuzey Çin'den geçen, "özofagus kanser kuşağı" adı verilen bölgededir (3). Skuamoz hücreli karsinom ve adenokarsinom olmak üzere iki histolojik alt tipi vardır. 1960'lı yıllarda tüm Özofagus kanserlerinin %90'ını skuamöz hücreli karsinom oluştururken adenokarsinom sıklığı hızlı bir artış göstermiştir. Skuamoz hücreli karsinom (SHK) proksimal özofagusta yerleşim gösteren ve daha kötü prognozlu tipidir. Yüksek riskli bölgelerde SHK daha sıktır ancak SHK için risk faktörü olan sigara, alkol gibi alışkanlıklar bu bölgelerde sık değildir, muhtemel sebep kötü beslenme, meyve sebze tüketiminin az olması ve yüksek sıcaklıktaki içeceklerin tüketilmesi sebep olarak gösterilebilir (4, 5). 2015 Türkiye birleşik veri tabanına göre ülkemizde en sık Van ve çevresine görülmekte ve en sık görülen ilk 10 kanser arasında yer almamaktadır.

Etiyoloji

Skuamoz hücreli karsinom için başlıca risk faktörleri sigara ve alkol kullanımı, meyve ve sebzeden fakir diyet, yüksek ısıdaki içeceklerin tüketilmesidir. Human papilloma virus enfeksiyonu da üst özofagusta skuamoz hücreli kanser gelişimi ile ilişkilidir. Akalazya, kostik striktürler, gastrektomi ve atrofik gastrit gibi anatomik bozukluklar da artmış SHK riski ile ilişkilidir. Tylosis (palmoplantar keratozis), Bloom sendromu, Fanconi anemisi gibi bazı genetik sendromlarda da SHK riski artmıştır. Bu tür sendromlarda endoskopi ile tarama düşünülebilir (6).

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kanserleri ile ilgili henüz yayınlanmış veri bulunmamaktadır (71, 72).

Ramucirumab bir VEGFR-2 monoklonal antikorudur. İleri gastrik ve özofagogastrik bileşke kanserlerinde ilk sıra kemoterapi sonrasında ramucirumabın plasebo ile karşılaştırıldığı REGARD çalışmasında genel sağ kalımda anlamlı artış gözlenmiştir (5,2 ay / 38 ay, p=0047)(73). RAINBOW çalışmasında ise metastatik gastrik ve özofagogastrik bileşke kanserlerinde ilk sıra kemoterapide paklitaksele eklendiğinde ortalama sağ kalım anlamlı olarak uzun bulunmuştur (9,6 ay/7,3 ay, p<0,0001) (74). Bu çalışmalar ışığında kılavuzlar ramucirumabı özofagogastrik bileşke (kategori 1) ve özofageal (kategori 2A) adenokarsinomlarda tek başına ya da paklitakselle kombine olarak ikinci sıra ve sonrasında önermektedir. FOLFİRİ ile de kullanılabilir (kategori 2B).

Dosetaksel, paklitaksel, irinotekan monoterapisi ve FOLFİRİ de 2. Basamakta önerilen diğer tedavilerdir.

Trifluridin ve tipirasil rekürren ve metastatik özofagogastrik bileşke kanserlerinde 3. basamakta önerilir, ancak düşük tümör yükü olan ve hap içme konusunda problemi olmayan seçilmiş hastalarda düşünülebilir.

Trastuzumab deruxtekan(T-DXd), trastuzumab ile bir topoizomeraz inhibitörü olan deruxtecandan oluşan bir ilaç-antikor konjugatıdır. En az 2 sıra kemoterapi almış, progrese olan gastrik ve özofagosgastrik bileşke kanserlerinde trastuzumab deruxtecan ve kemoterapinin karşılaştırıldığı çalışmada T-DXd kolunda yanıt oranı (%51-%14) ve genel sağ kalım (12,5 ay-8,4 ay) anlamlı olarak yüksek bulunmuştur (75). Bu çalışmada nötropeni, lökopeni ve anemi T-DXd kolunda kemoterapi kolundan daha yüksek oranda gözlenmiş ve T-DXd alan 125 hastanın 12'sinde ilaca bağlı akciğer toksisitesi görülmüştür.

Tedaviye yanıtın değerlendirilmesi

FDG-PET/CT kemoradyoterapi sonrası metastazların değerlendirilmesi açısından yararlıdır (76, 77). Tedavi tamamlandıktan en az 5-8 hafta sonra yapılmalı. Toraks+abdomen (ve gerekirse pelvik) BT ile de değerlendirme yapılabilir. Üst gastrointestinal endoskopi de definitif kemoradyoterapi sonrası patolojik yanıtın değerlendirilmesi için önerilir ancak cerrahi planlanıyorsa yapılmayabilir.

Takip

Preoperatif kemoradyoterapi almamış hastada özofajektomi sonrası rezeksiyon sınırları temizse hasta takibe alınır ancak R1 ya da R2 rezeksiyon yapıldıysa kemoradyoterapi başlanır. Preoperatif KRT sonrası opere olan hastada R0 rezeksiyon yapıldıysa takip, R1-R2 rezeksiyon yapıldıysa progresyon gözlenir ya da palyatif bakım uygulanır.

Kaynaklar

1. World Health Organisation. İnternational Agency for Research on Cancer. GLOBOCAN 2018: oesopagus cancer fact sheet 2018.
2. Torre LA, Siegel RL, Ward E M, et al. Global Cancer Incidence and Mortality Rates and Trends- an update. Cancer Epidemiol Biomarkers Prev. 2016;25:16-27.
3. Zhao JK, Wu M, Kim CH, et al. Jiangsu Four Cancers Study: a large case-control study of lung, liver, stomach, and eosophageal cancers in Jiangsu Province, China. Eus J Cancer Prev. 2017;26:357-364.
4. Islami F, Pourshams A, Nasrollahzadeh D, et al. Tea drinking habits and oesophageal cancer in a high risk area in northern Iran: population based case–control study. BMJ. 2009;26;338:b929.
5. Rasool S, A Ganai B, Syed Sameer A, et al. Esophageal cancer: associated factors with special reference to the Kashmir Valley. Tumori 2012;98:191–203.
6. Ellis A, Field JK, Field EA, et al. Tylosis associated with carcinoma of the oesophagus and oral leukoplakia in a large Liverpool family--a review of six generations. Eur J Cancer B Oral Oncol. 1994;30B(2):102-112.
7. Amin, M.B., Edge, S.B., Greene, F.L. (2017). AJCC cancer staging manuel (ed. 8). New York, NY, Springer.

8. Rice TW, Apperson-Hansen C, DiPaola LM, et al. Worldwide Esophageal Cancer Collaboration: clinical staging data. Dis Esophagus. 2016;29(7):707–714.
9. Sun XD, Yu JM, Fan XL, et al. Randomized clinical study of surgery versus radiotherapy alone in the treatment of resectable esophageal cancer in the chest. Zhonghua Zhong Liu Za Zhi. 2006;28(10):784-787.
10. Coccolini F, Nardi M, Montori G, et al. Neoadjuvant chemotherapy in advanced gastric and esophago-gastric cancer. Meta-analysis of randomized trials. Int J Surg. 2018;51:120-127.
11. Yang H, Liu H, Chen Y, et al. Neoadjuvant Chemoradiotherapy Followed by Surgery Versus Surgery Alone for Locally Advanced Squamous Cell Carcinoma of the Esophagus (NEOCRTEC5010): A Phase III Multicenter, Randomized, Open-Label Clinical Trial. J Clin Oncol. 2018;36(27):2796-2803.
12. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074-2084.
13. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectabl gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol. 2011;29:1715-1721.
14. Anderson D, Cunningham D, Nankivell M, et al. Neoadjuvant cisplatin and fluorouracil versus epirubicin, cisplatin, and capecitabine followed by resection in patients with oesophageal adenocarcinoma (UK MRC OE05): an open-label, randomised phase 3 trial. Lancet Oncol. 2017;18(9):1249-1260.
15. 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):725-730.
16. Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol. 2002;20(5):1167-1174.
17. Shapiro J, van Lanschot JJB, Hulshof MCCM, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16(9):1090-1098.
18. Herskovic A, Martz K, al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med. 1992;326(24):1593-1598.
19. Ilson DH, Wadleigh RG, Leichman LP, et al. Paclitaxel given by a weekly 1-h infusion in advanced esophageal cancer. Ann Oncol. 2007;18:898-902.
20. Muro K, Hamaguchi T, Ohtsu A, et al. A phase II study of single-agent docetaxel in patients with metastatic esophageal cancer. Ann Oncol. 2004;15:955-959.
21. Mavroudis D, Kourousis C, Androulakis N, et al. Frontline treatment of advanced gastric cancer with docetaxel and granulocyte colony-stimulating factor (G-CSF): a phase II trial. Am J Clin Oncol. 2000; 23:341-344.
22. Kato K, Tahara M, Hironaka S, et al. A phase II study of paclitaxel by weekly 1-h infusion for advanced or recurrent esophageal cancer in patients who had previously received platinum-based chemotherapy. Cancer Chemother Pharmacol. 2011;67:1265-1272.
23. Kii T, Takiuchi H, Gotoh M, et al. [Weekly administration regimen of paclitaxel (PTX) in patient with inoperable or recurrent gastric cancer]. Gan To Kagaku Ryoho. 2006;33:621-624.
24. Köhne CH, Catane R, Klein B, et al. Irinotecan is active in chemonaive patients with metastatic gastric cancer: a phase II multicentric trial. Br J Cancer. 2003;89:997-1001.
25. Enzinger PC, Kulke MH, Clark JW, et al. A phase II trial of irinotecan in patients with previously untreated advanced esophageal and gastric adenocarcinoma. Dig Dis Sci. 2005;50:2218-2223.
26. Hong YS, Song SY, Lee SI, et al. A phase II trial of capecitabine in previously untreated patients with advanced and/or metastatic gastric cancer. Ann Oncol. 2004;15:1344-1347.
27. Shirasaka T, Shimamato Y, Ohshimo H, et al. Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. Anticancer Drugs. 1996;7:548-557.
28. Boku N, Yamamoto S, Fukuda H, et al. Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol. 2009;10:1063-1069.
29. Lee JL, Kang YK, Kang HJ, et al. A randomised multicentre phase II trial of capecitabine vs S-1 as first-line treatment in elderly patients with metastatic or recurrent unresectable gastric cancer. Br J Cancer. 2008;99:584-590.
30. 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):1435-1442.
31. Montagnani F, Turrisi G, Marinozzi C, et al. Effectiveness and safety of oxaliplatin compared to cisplatin for advanced, unresectable gastric cancer: a systematic review and meta-analysis. Gastric Cancer. 2011;14:50-55.
32. Hall PS, Swinson D, Waters JS, et al. Optimizing chemotherapy for frail and elderly patients (pts) with advanced gastroesophageal cancer (aGOAC): The GO2 phase III trial. Journal of Clinical Oncology. 2019;37:4006.
33. Enzinger PC, Burtness B, Hollis D, et al. CALGB 80403/ECOG 1206: A randomized phase II study of three standard chemotherapy regimens (ECF, IC, FOLFOX) plus cetuximab in metastatic esophageal and GE junction cancer. J Clin Oncol. 2010; 28S: ASCO #4006.
34. Park H, Jin RU, Wang-Gillam A, et al. FOLFIRINOX for the Treatment of Advanced Gastroesophageal Cancers: A Phase 2 Nonrandomized Clinical Trial. JAMA Oncol. 2020;6(8):1231-1240.

35. Bleiberg H, Conroy T, Paillot B, et al. Randomised phase II study of cisplatin and 5-fluorouracil (5-FU) versus cisplatin alone in advanced squamous cell oesophageal cancer. Eur J Cancer. 1997;33:1216-1220.
36. Okines AFC, Norman AR, McCloud P, et al. Meta-analysis of the REAL-2 and ML17032 trials: evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer. Ann Oncol. 2009;20:1529-1534.
37. Guimbaud R, Louvet C, Ries P, et al. Prospective, randomized, multicenter, phase III study of fluorouracil, leucovorin, and irinotecan versus epirubicin, cisplatin, and capecitabine in advanced gastric adenocarcinoma: a French intergroup (Fédération Francophone de Cancérologie Digestive, Fédération Nationale des Centres de Lutte Contre le Cancer, and Groupe Coopérateur Multidisciplinaire en Oncologie) study. J Clin Oncol. 2014;32:3520-3526
38. Oh SC, Sur HY, Sung HJ, et al. A phase II study of biweekly dose-intensified oral capecitabine plus irinotecan (bXELIRI) for patients with advanced or metastatic gastric cancer. Br J Cancer. 2007;96:1514-1519.
39. Luo HY, Wang ZQ, Wang FH, et al. Phase 2 study of capecitabine and irinotecan combination chemotherapy (modified XELIRI regimen) in patients with advanced gastric cancer. Am J Clin Oncol. 2011;34:555-560.
40. Narahara H, Iishi H, Imamura H, et al. Randomized phase III study comparing the efficacy and safety of irinotecan plus S-1 with S-1 alone as first-line treatment for advanced gastric cancer (study GC0301/TOP-002). Gastric Cancer. 2011;14:72-80.
41. Findlay M, Cunningham D, Norman A, et al. A phase II study in advanced gastro-esophageal cancer using epirubicin and cisplatin in combination with continuous infusion 5-fluorouracil (ECF). Ann Oncol. 1994;5:609-616.
42. Webb A, Cunningham D, Scarffe JH, et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. J Clin Oncol. 1997;15:261-267.
43. GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group, Oba K, Paoletti X, et al. Role of chemotherapy for advanced/recurrent gastric cancer: an individual-patient-data meta-analysis. Eur J Cancer. 2013;49:1565-1577.
44. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol. 2006;24:4991-4997.
45. Thuss-Patience PC, Kretzschmar A, Repp M, et al. Docetaxel and continuous-infusion fluorouracil versus epirubicin, cisplatin, and fluorouracil for advanced gastric adenocarcinoma: a randomized phase II study. J Clin Oncol. 2005;23:494-501.
46. Al-Batran SE, Pauligk C, Homann N, et al. The feasibility of triple-drug chemotherapy combination in older adult patients with oesophagogastric cancer: a randomised trial of the Arbeitsgemeinschaft Internistische Onkologie (FLOT65+). Eur J Cancer. 2013;49:835-842.
47. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology. https://www.nccn.org/professionals/physician_gls (Accessed on November 09, 2021).
48. 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; 6:1571-1580.
49. 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;398:27-40.
50. Moehler M, Shitara K, Garrido M, et al. LBA6_PR - Nivolumab (nivo) plus chemotherapy (chemo) versus chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer (GC/GEJC)/esophageal adenocarcinoma (EAC): First results of the CheckMate 649 study. Ann Oncol 2020;31;S1191.
51. Chau I, Doki Y, Ajani JA, et al. Nivolumab (NIVO) plus ipilimumab (IPI) or NIVO plus chemotherapy (chemo) versus chemo as first-line (1L) treatment for advanced esophageal squamous cell carcinoma (ESCC): First results of the CheckMate 648 study (abstract). J Clin Oncol 39, 2021 (suppl 15; abstr LBA4001). (Accessed on June 11, 2021).
52. Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Lancet. 2021;398:759-771.
53. FDA approves pembrolizumab for esophageal or GEJ carcinoma. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-esophageal-or-gej-carcinoma?utm_medium=email&utm_source=govdelivery (Accessed on March 23, 2021).
54. N, Ryu MH, Oh D, et al. LBA7_PR - Nivolumab plus chemotherapy versus chemotherapy alone in patients with previously untreated advanced or recurrent gastric/gastroesophageal junction (G/GEJ) cancer: ATTRACTION-4 (ONO-4538-37) study. Ann Oncol 2020; 31S: ESMO #S1142.
55. 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;376:687-697.
56. Shah MA, Xu RH, Bang YJ, et al. HELOISE: Phase IIIb Randomized Multicenter Study Comparing

Standard-of-Care and Higher-Dose Trastuzumab Regimens Combined With Chemotherapy as First-Line Therapy in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma. J Clin Oncol. 2017;35:2558-2567.
57. Tabernero J, Hoff PM, Shen L, et al. Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): final analysis of a double-blind, randomised, placebo-controlled phase 3 study. Lancet Oncol. 2018;19:1372-1384.
58. Janjigian YY, Maron SB, Chatila WK, et al. First-line pembrolizumab and trastuzumab in HER2-positive oesophageal, gastric, or gastro-oesophageal junction cancer: an open-label, single-arm, phase 2 trial. Lancet Oncol. 2020;21:821-831.
59. Janjigian YY, Kawazoe A, Yanez PE, et al. Pembrolizumab plus trastuzumab and chemotherapy for HER2+ metastatic gastric or gastroesophageal junction (G/GEJ) cancer: Initial findings of the global phase 3 KEYNOTE-811 study (abstract). J clin Oncol 39, 2021 (suppl 15; abstr 4013).
60. Updated United States Food and Drug Administration-approved prescribing information for pembrolizumab available online at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s097lbl.pdf (Accessed on May 06, 2021).
61. Makiyama A, Sukawa Y, Kashiwada T, et al. Randomized, phase II study of trastuzumab beyond progression in patients with HER2-positive advanced gastric or gastroesophageal junction cancer: WJOG7112G (T-ACT Study). J Clin Oncol. 2020;38:1919-1927.
62. Hecht JR, Bang YJ, Qin SK, et al. Lapatinib in Combination With Capecitabine Plus Oxaliplatin in Human Epidermal Growth Factor Receptor 2-Positive Advanced or Metastatic Gastric, Esophageal, or Gastroesophageal Adenocarcinoma: TRIO-013/LOGiC--A Randomized Phase III Trial. J Clin Oncol. 2016;34:443-451.
63. Dijksterhuis WPM, Verhoeven RHA, Slingerland M, et al. Heterogeneity of first-line palliative systemic treatment in synchronous metastatic esophagogastric cancer patients: A real-world evidence study. Int J Cancer. 2020;146:1889-1901.
64. Ter Veer E, Haj Mohammad N, van Valkenhoef G, et al. The Efficacy and Safety of First-line Chemotherapy in Advanced Esophagogastric Cancer: A Network Meta-analysis. J Natl Cancer Inst. 2016;108.
65. Kato K, Cho BC, Takahashi M, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20:1506-1517.
66. Fuchs CS, Doi T, Jang RW, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE- 059 trial. JAMA Oncol. 2018;4:e180013.
67. Kojima T, Shah MA, Muro K. Randomized Phase III KEYNOTE-181 Study of Pembrolizumab Versus Chemotherapy in Advanced Esophageal Cancer. J Clin Oncol. 2020;38(35):4138-4148.
68. Shah MA, Kojima T, Hochhauser D, et al. Efficacy and safety of pembrolizumab for heavily pretreated patients with advanced, metastatic adenocarcinoma or squamous cell carcinoma of the esophagus: the phase 2 KEYNOTE-180 study. JAMA Oncol. 2018;5:546-550.
69. Bang Y-J, Muro K, Fuchs CS, et al. KEYNOTE-059 cohort 2: safety and efficacy of pembrolizumab (pembro) plus 5-fluorouracil (5-FU) and cisplatin for first-line (1L) treatment of advanced gastric cancer. J Clin Oncol. 2017;35:4012.
70. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol. 2020;21:271-282.
71. Arnold A, Daum S, von Winterfeld M, et al. Analysis of NTRK expression in gastric and esophageal adenocarcinoma (AGE) with pan- TRK immunohistochemistry. Pathol Res Pract. 2019;215:152662.
72. Shinozaki-Ushiku A, Ishikawa S, Komura D, et al. The first case of gastric carcinoma with NTRK rearrangement: identification of a novel ATP1B-NTRK1 fusion. Gastric Cancer. 2020;23:944-947.
73. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2014;383:31-39.
74. Wilke H, Muro K, Van Cutsem E, 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;15:1224-1235.
75. Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. N Engl J Med. 2020;382(25):2419-2430.
76. Munden RF, Macapinlac HA, Erasmus JJ. Esophageal cancer: the role of integrated CT-PET in initial staging and response assessment after preoperative therapy. J Thorac Imaging. 2006;21:137-145.
77. van Westreenen HL, Westerterp M, Bossuyt PMM, et al. Systematic review of the staging performance of 18F-fluorodeoxyglucose positron emission tomography in esophageal cancer. J Clin Oncol. 2004;22:3805-3812.