

METASTATİK MİDE TÜMÖRLERİNE YAKLAŞIM

32. BÖLÜM

Derya Salim UYMAZ¹

ÖZET

Mide kanseri, dünyadaki görülme sıklığı azalmasına rağmen, düşük sağkalım oranı nedeni ile hala önemli bir sağlık problemidir. Düşük sağkalımın en önemli sebeplerinden biri hastaların başvuru sırasında ileri evre olmalarıdır. Metastatik mide tümörleri için standart tedavi palyatif kemoterapi ve destekleyici bakım olmasına rağmen kemoterapi tedavisi avantajlarına rağmen tatmin edici sonuçlar vermemektedir. Bu nedenle metastatik mide tümörü yönetiminde değişik alternatif tedavi yöntemleri denenmektedir. Karaciğere yönelik tedaviler arasında rezeksiyon, radyofrekans ablasyon, mikrodalga ablasyon, hepatik arter infüzyon kemoterapisi varken peritoneal metastaz durumlarında sitoredüktif cerrahiye takiben intraperitoneal kemoterapi, paraaortik lenf nodu metastazlarında ise paraaortik lenf nodu diseksiyonu tedavi seçenekleri arasındadır. Lokal ve sistemik tedavilerin kombine edilmesi ve bu yöndeki çalışmaların artması ile metastatik mide tümörlerine karşı yaklaşımlar zamanla değişiklik gösterecektir.

GİRİŞ

Mide kanseri dünya çapında önemli bir sağlık sorunu olmaya devam etmektedir ve hematogen metastaz, lenfatik metastaz veya periton tohumlanması gibi çeşitli yollarla yayılma potansiyeli olan dinamik bir hastalık olarak kabul edilmektedir (1,4). Mide kanserinin göreceli olarak agresif davranışı, hastalığın erken evrelerinde bile metastaza neden olabilir ve metastazlar aynı anda birden fazla odağı etkileyebilir (5,6).

Onlarca yıl önce, metastatik mide kanseri (MMK) için tek tedavi seçeneği destekleyici bakımdı. Çeşitli kanser türlerinde sitotoksik kemoterapi ajanlarının artan kullanımıyla birlikte,

MMK için de kemoterapi kullanılmaya başlanmıştır ve çeşitli çalışmalar, sistemik kemoterapinin destekleyici bakıma üstünlüğünü göstermiştir (7,9). İyi bilinen çalışmalardan biri 1997'de yayınlandı ve kemoterapi grubuna randomize edilen hastalar için genel sağkalım (GS), ilerlemiş mide kanserinde en iyi destekleyici bakıma kıyasla daha uzun olma eğilimindeydi (8'e karşı 5 ay; istatistiksel olarak anlamlı değil) (7). Çalışmada, sistemik kemoterapi, daha uzun kalitede sağkalım (medyan 6'ya karşı 2 ay) ve hastalığın ilerlemesi için daha uzun süre (medyan 6'ya karşı 2 ay) sağladı. Hayatta kalma ve yaşam kalitesi ile ilgili ilk çalışmaların olumlu sonuçlarının ardından, çok ajanlı rejimlerden oluşan palyatif

¹ Uzm. Dr. Derya Salim UYMAZ, Koç Üniversitesi Genel Cerrahi AD, deryauymaz@yahoo.com

ilerlemiş mide kanserli hastalarda R0 elde edildiğinde daha iyi sağkalım sağlayabileceği sonucuna varmışlardır.

Yeni bir kavram olarak dönüşüm cerrahisi, ileriye dönük çalışmalarla klinik değerlendirmeyi gerektirir. Birkaç Koreli, Japon ve Çinli iş birliği grubu tarafından yürütülen büyük bir kohortun sonuçları, MMK'nin yönetiminde dönüşüm terapisinin gelecekteki rolünü belirleyecektir (131).

SONUÇLAR

MMK, mide kanserinin agresif biyolojisi nedeniyle sıklıkla karşılaşılan bir sorundur. MMK için standart tedavi sistemik kemoterapidir. Ancak, MMK tek bir antite değildir ve sonuçları iyileştirmek için mide kanseri yönetiminde bazı perspektif değişikliklerine ihtiyaç vardır. Çalışmalar, özellikle karaciğer, periton ve para-aortik lenf nodu metastazı ile ilgili olanlar, seçilmiş hasta gruplarında kişiselleştirilmiş bir yaklaşımın faydalarını göstermiştir. Bu nedenle, mevcut literatür ışığında, MMK'li tüm hastalar umutsuz olarak değerlendirilmemeli ve deneyimli merkezlerde multidisipliner yaklaşımın bir parçası olarak, bu tür hastalar için olası kombine sistemik ve lokal tedavi seçenekleri bireysel olarak düşünülmelidir.

KAYNAKLAR

1. Kakeji Y, Morita M, Maehara Y. Strategies for treating liver metastasis from gastric cancer. *Surg Today* 2010;40:287-94. [Crossref] [PubMed]
2. Choi YY, An JY, Guner A, et al. Skip lymph node metastasis in gastric cancer: is it skipping or skipped? *Gastric Cancer* 2016;19:206-15. [Crossref] [PubMed]
3. Zhu T, Hu X, Wei P, et al. Molecular background of the regional lymph node metastasis of gastric cancer. *Oncol Lett* 2018;15:3409-14. [PubMed]
4. Li W, Ng JM, Wong CC, et al. Molecular alterations of cancer cell and tumour microenvironment in metastatic gastric cancer. *Oncogene* 2018;37:4903-20. [Crossref] [PubMed]
5. Koder Y. Surgery with curative intent for stage IV gastric cancer: Is it a reality of illusion? *Ann Gastroenterol Surg* 2018;2:339-47. [Crossref] [PubMed]
6. Guner A. Recent trends of gastric cancer treatment in Turkey. *Transl Gastroenterol Hepatol* 2017;2:31. [Crossref] [PubMed]
7. Glimelius B, Ekstrom K, Hoffman K, et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Ann Oncol* 1997;8:163-8. [Crossref] [PubMed]
8. Pyrhönen S, Kuitunen T, Nyandoto P, et al. Randomized comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. *Br J Cancer* 1995;71:587-91. [Crossref] [PubMed]
9. Murad AM, Santiago FF, Petroianu A, et al. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. *Cancer* 1993;72:37-41. [Crossref] [PubMed]
10. Japanese Gastric Cancer A. Japanese gastric cancer treatment guidelines 2014 (ver. 4). *Gastric Cancer* 2017;20:1-19. [Crossref] [PubMed]
11. Ajani JA, D'Amico TA, Almhanna K, et al. Gastric Cancer, Version 3.2016, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2016;14:1286-312. [Crossref] [PubMed]
12. Keränen I, Kylanpää L, Udd M, et al. Gastric outlet obstruction in gastric cancer: a comparison of three palliative methods. *J Surg Oncol* 2013;108:537-41. [Crossref] [PubMed]
13. Müsri FY, Mutlu H, Karaagac M, et al. Primary Tumor Resection and Survival in Patients with Stage IV Gastric Cancer. *J Gastric Cancer* 2016;16:78-84. [Crossref] [PubMed]
14. He MM, Zhang DS, Wang F, et al. The role of non-curative surgery in incurable, asymptomatic advanced gastric cancer. *PLoS One* 2013;8:e83921. [Crossref] [PubMed]
15. Yamamoto Y, Yoshikawa T, Morinaga S, et al. Significance of volume-reduction surgery for far-advanced gastric cancer during treatment with novel anticancer agents. *Int J Clin Oncol* 2009;14:225-9. [Crossref] [PubMed]
16. Sun J, Song Y, Wang Z, et al. Clinical significance of palliative gastrectomy on the survival of patients with incurable advanced gastric cancer: a systematic review and meta-analysis. *BMC Cancer* 2013;13:577. [Crossref] [PubMed]
17. Tiberio GA, Ministrini S, Gardini A, et al. Factors influencing survival after hepatectomy for metastases from gastric cancer. *Eur J Surg Oncol* 2016;42:1229-35. [Crossref] [PubMed]
18. Lasithiotakis K, Antoniou SA, Antoniou GA, et al. Gastrectomy for stage IV gastric cancer. a systematic review and meta-analysis. *Anticancer Res* 2014;34:2079-85. [PubMed]
19. Fujitani K, Yang H-K, 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;17:309-18. [Crossref] [PubMed]
20. Zurleni T, Gjoni E, Altomare M, et al. Conversion surgery for gastric cancer patients: A review. *World J Gastrointest Oncol* 2018;10:398-409. [Crossref] [PubMed]

21. D'Ugo D, Cananzi FCM, Persiani R, et al. REGATTA trial: a call for the USA and Europe. *Lancet Oncol* 2016;17:261-2. [Crossref] [PubMed]
22. Qiu MZ, Shi SM, Chen ZH, et al. Frequency and clinicopathological features of metastasis to liver, lung, bone, and brain from gastric cancer: A SEER-based study. *Cancer Med* 2018;7:3662-72. [Crossref] [PubMed]
23. D'Angelica M, Gonen M, Brennan MF, et al. Patterns of initial recurrence in completely resected gastric adenocarcinoma. *Ann Surg* 2004;240:808-16. [Crossref] [PubMed]
24. Yoo CH, Noh SH, Shin DW, et al. Recurrence following curative resection for gastric carcinoma. *Br J Surg* 2000;87:236-42. [Crossref] [PubMed]
25. Guner A, Son T, Cho I, et al. Liver-directed treatments for liver metastasis from gastric adenocarcinoma: comparison between liver resection and radiofrequency ablation. *Gastric Cancer* 2016;19:951-60. [Crossref] [PubMed]
26. Hwang JE, Kim SH, Jin J, et al. Combination of percutaneous radiofrequency ablation and systemic chemotherapy are effective treatment modalities for metachronous liver metastases from gastric cancer. *Clin Exp Metastasis* 2014;31:25-32. [Crossref] [PubMed]
27. Lee JW, Choi MH, Lee YJ, et al. Radiofrequency ablation for liver metastases in patients with gastric cancer as an alternative to hepatic resection. *BMC Cancer* 2017;17:185. [Crossref] [PubMed]
28. Zhou F, Yu XL, Liang P, et al. Microwave ablation is effective against liver metastases from gastric adenocarcinoma. *Int J Hyperthermia* 2017;33:830-5. [PubMed]
29. Martella L, Bertozzi S, Londero AP, et al. Surgery for Liver Metastases From Gastric Cancer: A Meta-Analysis of Observational Studies. *Medicine (Baltimore)* 2015;94:e1113. [Crossref] [PubMed]
30. Liu SF, Lu CR, Cheng HD, et al. Comparison of Therapeutic Efficacy between Gastrectomy with Transarterial Chemoembolization Plus Systemic Chemotherapy and Systemic Chemotherapy Alone in Gastric Cancer with Synchronous Liver Metastasis. *Chin Med J (Engl)* 2015;128:2194-201. [Crossref] [PubMed]
31. Fukami Y, Kaneoka Y, Maeda A, et al. Adjuvant hepatic artery infusion chemotherapy after hemihepatectomy for gastric cancer liver metastases. *Int J Surg* 2017;46:79-84. [Crossref] [PubMed]
32. Yamakado K, Nakatsuka A, Takaki H, et al. Prospective study of arterial infusion chemotherapy followed by radiofrequency ablation for the treatment of liver metastasis of gastric cancer. *J Vasc Interv Radiol* 2005;16:1747-51. [Crossref] [PubMed]
33. Lewis GD, Chiang SB, Butler EB, et al. The utility of positron emission tomography/computed tomography in target delineation for stereotactic body radiotherapy for liver metastasis from primary gastric cancer: an illustrative case report and literature review. *J Gastrointest Oncol* 2017;8:E39-42. [Crossref] [PubMed]
34. Goodman KA, Wiegner EA, Maturen KE, et al. Dose-escalation study of single-fraction stereotactic body radiotherapy for liver malignancies. *Int J Radiat Oncol Biol Phys* 2010;78:486-93. [Crossref] [PubMed]
35. Cheon SH, Rha SY, Jeung HC, et al. Survival benefit of combined curative resection of the stomach (D2 resection) and liver in gastric cancer patients with liver metastases. *Ann Oncol* 2008;19:1146-53. [Crossref] [PubMed]
36. Ambiru S, Miyazaki M, Ito H, et al. Benefits and limits of hepatic resection for gastric metastases. *Am J Surg* 2001;181:279-83. [Crossref] [PubMed]
37. Okano K, Maeba T, Ishimura K, et al. Hepatic resection for metastatic tumors from gastric cancer. *Ann Surg* 2002;235:86-91. [Crossref] [PubMed]
38. Zacherl J, Zacherl M, Scheuba C, et al. Analysis of hepatic resection of metastasis originating from gastric adenocarcinoma. *J Gastrointest Surg* 2002;6:682-9. [Crossref] [PubMed]
39. Shirabe K, Wakiyama S, Gion T, et al. Hepatic resection for the treatment of liver metastases in gastric carcinoma: review of the literature. *HPB (Oxford)* 2006;8:89-92. [Crossref] [PubMed]
40. Sakamoto Y, Ohyama S, Yamamoto J, et al. Surgical resection of liver metastases of gastric cancer: an analysis of a 17-year experience with 22 patients. *Surgery* 2003;133:507-11. [Crossref] [PubMed]
41. Koga R, Yamamoto J, Ohyama S, et al. Liver resection for metastatic gastric cancer: experience with 42 patients including eight long-term survivors. *Jpn J Clin Oncol* 2007;37:836-42. [Crossref] [PubMed]
42. Thelen A, Jonas S, Benckert C, et al. Liver resection for metastatic gastric cancer. *Eur J Surg Oncol* 2008;34:1328-34. [Crossref] [PubMed]
43. Morise Z, Sugioka A, Hoshimoto S, et al. The role of hepatectomy for patients with liver metastases of gastric cancer. *Hepatogastroenterology* 2008;55:1238-41. [PubMed]
44. Garancini M, Uggeri F, Degrate L, et al. Surgical treatment of liver metastases of gastric cancer: is local treatment in a systemic disease worthwhile? *HPB (Oxford)* 2012;14:209-15. [Crossref] [PubMed]
45. Makino H, Kunisaki C, Izumisawa Y, et al. Indication for hepatic resection in the treatment of liver metastasis from gastric cancer. *Anticancer Res* 2010;30:2367-76. [PubMed]
46. Miki Y, Fujitani K, Hirao M, et al. Significance of surgical treatment of liver metastases from gastric cancer. *Anticancer Res* 2012;32:665-70. [PubMed]
47. Chen L, Song MQ, Lin HZ, et al. Chemotherapy and resection for gastric cancer with synchronous liver metastases. *World J Gastroenterol* 2013;19:2097-103. [Crossref] [PubMed]
48. Tiberio GA, Baiocchi GL, Morgagni P, et al. Gastric cancer and synchronous hepatic metastases: is it possible to recognize candidates to R0 resection? *Ann Surg Oncol* 2015;22:589-96. [Crossref] [PubMed]
49. Oki E, Tokunaga S, Emi Y, et al. Surgical treatment of liver metastasis of gastric cancer: a retrospective multicenter cohort study (KSCC1302). *Gastric Cancer* 2016;19:968-76. [Crossref] [PubMed]
50. Tatsubayashi T, Tanizawa Y, Miki Y, et al. Treatment outcomes of hepatectomy for liver metastases of gastric

- cancer diagnosed using contrast-enhanced magnetic resonance imaging. *Gastric Cancer* 2017;20:387-93. [Crossref] [PubMed]
51. Ministrini S, Solaini L, Cipollari C, et al. Surgical treatment of hepatic metastases from gastric cancer. *Updates Surg* 2018;70:273-8. [Crossref] [PubMed]
 52. Chen J, Tang Z, Dong X, et al. Radiofrequency ablation for liver metastasis from gastric cancer. *Eur J Surg Oncol* 2013;39:701-6. [Crossref] [PubMed]
 53. Liao YY, Peng NF, Long D, et al. Hepatectomy for liver metastases from gastric cancer: a systematic review. *BMC Surg* 2017;17:14. [Crossref] [PubMed]
 54. Kerkar SP, Kemp CD, Avital I. Liver resections in metastatic gastric cancer. *HPB (Oxford)* 2010;12:589-96. [Crossref] [PubMed]
 55. Tiberio GA, Roviello F, Donini A, et al. Surgery for liver metastasis from gastric cancer. *Transl Gastroenterol Hepatol* 2016;1:68. [Crossref] [PubMed]
 56. Gadde R, Tamariz L, Hanna M, et al. Metastatic gastric cancer (MGC) patients: Can we improve survival by metastasectomy? A systematic review and meta-analysis. *J Surg Oncol* 2015;112:38-45. [Crossref] [PubMed]
 57. Petrelli F, Coinu A, Cabiddu M, et al. Hepatic resection for gastric cancer liver metastases: A systematic review and meta-analysis. *J Surg Oncol* 2015;111:1021-7. [Crossref] [PubMed]
 58. Markar SR, Mikhail S, Malietzis G, et al. Influence of Surgical Resection of Hepatic Metastases From Gastric Adenocarcinoma on Long-term Survival: Systematic Review and Pooled Analysis. *Ann Surg* 2016;263:1092-101. [Crossref] [PubMed]
 59. Puijk RS, Ruarus AH, Vroomen L, et al. Colorectal liver metastases: surgery versus thermal ablation (COLLISION) - a phase III single-blind prospective randomized controlled trial. *BMC Cancer* 2018;18:821. [Crossref] [PubMed]
 60. Kotewall CN, Cheung TT, She WH, et al. The role of radiofrequency ablation to liver transection surface in patients with close tumor margin of HCC during hepatectomy-a case matched study. *Transl Gastroenterol Hepatol* 2017;2:33. [Crossref] [PubMed]
 61. De Cobelli F, Marra P, Ratti F, et al. Microwave ablation of liver malignancies: comparison of effects and early outcomes of percutaneous and intraoperative approaches with different liver conditions: New advances in interventional oncology: state of the art. *Med Oncol* 2017;34:49. [Crossref] [PubMed]
 62. Kim HR, Cheon SH, Lee KH, et al. Efficacy and feasibility of radiofrequency ablation for liver metastases from gastric adenocarcinoma. *Int J Hyperthermia* 2010;26:305-15. [Crossref] [PubMed]
 63. Correa-Gallego C, Fong Y, Gonen M, et al. A retrospective comparison of microwave ablation vs. radiofrequency ablation for colorectal cancer hepatic metastases. *Ann Surg Oncol* 2014;21:4278-83. [Crossref] [PubMed]
 64. Tang K, Liu Y, Dong L, et al. Influence of thermal ablation of hepatic metastases from gastric adenocarcinoma on long-term survival: Systematic review and pooled analysis. *Medicine (Baltimore)* 2018;97:e13525. [Crossref] [PubMed]
 65. Thomassen I, van Gestel YR, van Ramshorst B, et al. Peritoneal carcinomatosis of gastric origin: a population-based study on incidence, survival and risk factors. *Int J Cancer* 2014;134:622-8. [Crossref] [PubMed]
 66. Beeharry MK, Liu WT, Yao XX, et al. A critical analysis of the cytoreductive surgery with hyperthermic intraperitoneal chemotherapy combo in the clinical management of advanced gastric cancer: an effective multimodality approach with scope for improvement. *Transl Gastroenterol Hepatol* 2016;1:77. [Crossref] [PubMed]
 67. Desiderio J, Chao J, Melstrom L, et al. The 30-year experience-A meta-analysis of randomised and high-quality non-randomised studies of hyperthermic intraperitoneal chemotherapy in the treatment of gastric cancer. *Eur J Cancer* 2017;79:1-14. [Crossref] [PubMed]
 68. Seshadri RA, Glehen O. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in gastric cancer. *World J Gastroenterol* 2016;22:1114-30. [Crossref] [PubMed]
 69. Wei J, Wu ND, Liu BR. Regional but fatal: Intraperitoneal metastasis in gastric cancer. *World J Gastroenterol* 2016;22:7478-85. [Crossref] [PubMed]
 70. Hasovits C, Clarke S. Pharmacokinetics and pharmacodynamics of intraperitoneal cancer chemotherapeutics. *Clin Pharmacokinet* 2012;51:203-24. [Crossref] [PubMed]
 71. Sugarbaker PH. Peritoneal carcinomatosis: natural history and rational therapeutic interventions using intraperitoneal chemotherapy. *Cancer Treat Res* 1996;81:149-68. [Crossref] [PubMed]
 72. Sugarbaker PH, Stuart OA. Pharmacokinetic and phase II study of heated intraoperative intraperitoneal melphalan. *Cancer Chemother Pharmacol* 2007;59:151-5. [Crossref] [PubMed]
 73. Sugarbaker PH, Cunliffe WJ, Belliveau J, et al. Rationale for integrating early postoperative intraperitoneal chemotherapy into the surgical treatment of gastrointestinal cancer. *Semin Oncol* 1989;16:83-97. [PubMed]
 74. González-Moreno S. Peritoneal Surface Oncology: A progress report. *Eur J Surg Oncol* 2006;32:593-6. [Crossref] [PubMed]
 75. Aoyama T, Yoshikawa T, Hayashi T, et al. Risk factors for peritoneal recurrence in stage II/III gastric cancer patients who received S-1 adjuvant chemotherapy after D2 gastrectomy. *Ann Surg Oncol* 2012;19:1568-74. [Crossref] [PubMed]
 76. Roviello F, Marrelli D, de Manzoni G, et al. Prospective study of peritoneal recurrence after curative surgery for gastric cancer. *Br J Surg* 2003;90:1113-9. [Crossref] [PubMed]
 77. Koga S, Kaibara N, Iitsuka Y, et al. Prognostic significance of intraperitoneal free cancer cells in gastric cancer patients. *J Cancer Res Clin Oncol* 1984;108:236-8. [Crossref] [PubMed]
 78. Fujimoto S, Shrestha RD, Kokubun M, et al. Positive results of combined therapy of surgery and intraperitoneal hyperthermic perfusion for far-advanced

- gastric cancer. *Ann Surg* 1990;212:592-6. [Crossref] [PubMed]
79. Hamazoe R, Maeta M, Kaibara N. Intraperitoneal thermochemotherapy for prevention of peritoneal recurrence of gastric cancer. Final results of a randomized controlled study. *Cancer* 1994;73:2048-52. [Crossref] [PubMed]
 80. Koga S, Hamazoe R, Maeta M, et al. Prophylactic therapy for peritoneal recurrence of gastric cancer by continuous hyperthermic peritoneal perfusion with mitomycin C. *Cancer* 1988;61:232-7. [Crossref] [PubMed]
 81. Cocolini F, Cotte E, Glehen O, et al. Intraperitoneal chemotherapy in advanced gastric cancer. Meta-analysis of randomized trials. *Eur J Surg Oncol* 2014;40:12-26. [Crossref] [PubMed]
 82. Roviello F, Caruso S, Neri A, et al. Treatment and prevention of peritoneal carcinomatosis from gastric cancer by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: overview and rationale. *Eur J Surg Oncol* 2013;39:1309-16. [Crossref] [PubMed]
 83. Xu DZ, Zhan YQ, Sun XW, et al. Meta-analysis of intraperitoneal chemotherapy for gastric cancer. *World J Gastroenterol* 2004;10:2727-30. [Crossref] [PubMed]
 84. Mi DH, Li Z, Yang KH, et al. Surgery combined with intraoperative hyperthermic intraperitoneal chemotherapy (IHIC) for gastric cancer: a systematic review and meta-analysis of randomised controlled trials. *Int J Hyperthermia* 2013;29:156-67. [Crossref] [PubMed]
 85. Yonemura Y, Fujimura T, Nishimura G, et al. Effects of intraoperative chemohyperthermia in patients with gastric cancer with peritoneal dissemination. *Surgery* 1996;119:437-44. [Crossref] [PubMed]
 86. Fujimoto S, Takahashi M, Mutou T, et al. Improved mortality rate of gastric carcinoma patients with peritoneal carcinomatosis treated with intraperitoneal hyperthermic chemoperfusion combined with surgery. *Cancer* 1997;79:884-91. [Crossref] [PubMed]
 87. Yang XJ, Huang CQ, Suo T, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: final results of a phase III randomized clinical trial. *Ann Surg Oncol* 2011;18:1575-81. [Crossref] [PubMed]
 88. Glehen O, Gilly FN, Arvieux C, et al. Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. *Ann Surg Oncol* 2010;17:2370-7. [Crossref] [PubMed]
 89. Shimada S, Tanaka E, Marutsuka T, et al. Extensive intraoperative peritoneal lavage and chemotherapy for gastric cancer patients with peritoneal free cancer cells. *Gastric Cancer* 2002;5:168-72. [Crossref] [PubMed]
 90. Hall JJ, Loggie BW, Shen P, et al. Cytoreductive surgery with intraperitoneal hyperthermic chemotherapy for advanced gastric cancer. *J Gastrointest Surg* 2004;8:454-63. [Crossref] [PubMed]
 91. Glehen O, Schreiber V, Cotte E, et al. Cytoreductive surgery and intraperitoneal chemohyperthermia for peritoneal carcinomatosis arising from gastric cancer. *Arch Surg* 2004;139:20-6. [Crossref] [PubMed]
 92. Kuramoto M, Shimada S, Ikeshima S, et al. Extensive intraoperative peritoneal lavage as a standard prophylactic strategy for peritoneal recurrence in patients with gastric carcinoma. *Ann Surg* 2009;250:242-6. [Crossref] [PubMed]
 93. Yang XJ, Li Y, Yonemura Y. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy to treat gastric cancer with ascites and/or peritoneal carcinomatosis: Results from a Chinese center. *J Surg Oncol* 2010;101:457-64. [Crossref] [PubMed]
 94. Rudloff U, Langan RC, Mullinax JE, et al. Impact of maximal cytoreductive surgery plus regional heated intraperitoneal chemotherapy (HIPEC) on outcome of patients with peritoneal carcinomatosis of gastric origin: results of the GYMSSA trial. *J Surg Oncol* 2014;110:275-84. [Crossref] [PubMed]
 95. Magge D, Zenati M, Mavanur A, et al. Aggressive locoregional surgical therapy for gastric peritoneal carcinomatosis. *Ann Surg Oncol* 2014;21:1448-55. [Crossref] [PubMed]
 96. Topal B, Demey K, Topal H, et al. Cytoreductive surgery and Hyperthermic intra-operative peritoneal chemotherapy with Cisplatin for gastric peritoneal Carcinomatosis Monocentric phase-2 nonrandomized prospective clinical trial. *BMC Cancer* 2017;17:771. [Crossref] [PubMed]
 97. Rihuete Caro C, Manzanedo I, Pereira F, et al. Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with gastric cancer and peritoneal carcinomatosis. *Eur J Surg Oncol* 2018;44:1805-10. [Crossref] [PubMed]
 98. Kim DW, Park DG, Song S, et al. Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy as Treatment Options for Peritoneal Metastasis of Advanced Gastric Cancer. *J Gastric Cancer* 2018;18:296-304. [Crossref] [PubMed]
 99. Fujimoto S, Shrestha RD, Kokubun M, et al. Intraperitoneal hyperthermic perfusion combined with surgery effective for gastric cancer patients with peritoneal seeding. *Ann Surg* 1988;208:36-41. [Crossref] [PubMed]
 100. Yonemura Y, Fujimura T, Fushida S, et al. Hyperthermo-chemotherapy combined with cytoreductive surgery for the treatment of gastric cancer with peritoneal dissemination. *World J Surg* 1991;15:530-5. [Crossref] [PubMed]
 101. Ishigami H, Fujiwara Y, Fukushima R, et al. Phase III Trial Comparing Intraperitoneal and Intravenous Paclitaxel Plus S-1 Versus Cisplatin Plus S-1 in Patients With Gastric Cancer With Peritoneal Metastasis: PHOENIX-GC Trial. *J Clin Oncol* 2018;36:1922-9. [Crossref] [PubMed]
 102. Facchiano E, Scaringi S, Kianmanesh R, et al. Laparoscopic hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of malignant ascites secondary to unresectable peritoneal carcinomatosis from advanced gastric cancer. *Eur J Surg Oncol* 2008;34:154-8. [Crossref] [PubMed]

103. Yonemura Y, Elnemr A, Endou Y, et al. Multidisciplinary therapy for treatment of patients with peritoneal carcinomatosis from gastric cancer. *World J Gastrointest Oncol* 2010;2:85-97. [Crossref] [PubMed]
104. Yonemura Y, Endou Y, Shinbo M, et al. Safety and efficacy of bidirectional chemotherapy for treatment of patients with peritoneal dissemination from gastric cancer: Selection for cytoreductive surgery. *J Surg Oncol* 2009;100:311-6. [Crossref] [PubMed]
105. Girshally R, Demtroder C, Albayrak N, et al. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) as a neoadjuvant therapy before cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *World J Surg Oncol* 2016;14:253. [Crossref] [PubMed]
106. Gockel I, Jansen-Winkel B, Haase L, et al. Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) in Gastric Cancer Patients with Peritoneal Metastasis (PM): Results of a Single-Center Experience and Register Study. *J Gastric Cancer* 2018;18:379-91. [Crossref] [PubMed]
107. Canbay E, Torun BC, Torun ES, et al. Evolution of management in peritoneal surface malignancies. *Ulus Cerrahi Derg* 2015;32:203-7. [Crossref] [PubMed]
108. Sasako M, Sano T, Yamamoto S, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *N Engl J Med* 2008;359:453-62. [Crossref] [PubMed]
109. Baba M, Hokita S, Natsugoe S, et al. Paraaortic lymphadenectomy in patients with advanced carcinoma of the upper-third of the stomach. *Hepatogastroenterology* 2000;47:893-6. [PubMed]
110. Roviello F, Pedrazzani C, Marrelli D, et al. Super-extended (D3) lymphadenectomy in advanced gastric cancer. *Eur J Surg Oncol* 2010;36:439-46. [Crossref] [PubMed]
111. Yonemura Y, Wu CC, Fukushima N, et al. Randomized clinical trial of D2 and extended paraaortic lymphadenectomy in patients with gastric cancer. *Int J Clin Oncol* 2008;13:132-7. [Crossref] [PubMed]
112. Tokunaga M, Ohyama S, Hiki N, et al. Can superextended lymph node dissection be justified for gastric cancer with pathologically positive para-aortic lymph nodes? *Ann Surg Oncol* 2010;17:2031-6. [Crossref] [PubMed]
113. Fujimura T, Nakamura K, Oyama K, et al. Selective lymphadenectomy of para-aortic lymph nodes for advanced gastric cancer. *Oncol Rep* 2009;22:509-14. [Crossref] [PubMed]
114. Oyama K, Fushida S, Kinoshita J, et al. Efficacy of pre-operative chemotherapy with docetaxel, cisplatin, and S-1 (DCS therapy) and curative resection for gastric cancer with pathologically positive para-aortic lymph nodes. *J Surg Oncol* 2012;105:535-41. [Crossref] [PubMed]
115. Tsuburaya A, Mizusawa J, Tanaka Y, et al. Neoadjuvant chemotherapy with S-1 and cisplatin followed by D2 gastrectomy with para-aortic lymph node dissection for gastric cancer with extensive lymph node metastasis. *Br J Surg* 2014;101:653-60. [Crossref] [PubMed]
116. Ito S, Sano T, Mizusawa J, et al. A phase II study of pre-operative chemotherapy with docetaxel, cisplatin, and S-1 followed by gastrectomy with D2 plus para-aortic lymph node dissection for gastric cancer with extensive lymph node metastasis: JCOG1002. *Gastric Cancer* 2017;20:322-31. [Crossref] [PubMed]
117. Yoshikawa T, Rino Y, Yukawa N, et al. Neoadjuvant chemotherapy for gastric cancer in Japan: a standing position by comparing with adjuvant chemotherapy. *Surg Today* 2014;44:11-21. [Crossref] [PubMed]
118. Yoshikawa T, Sasako M, Yamamoto S, et al. Phase II study of neoadjuvant chemotherapy and extended surgery for locally advanced gastric cancer. *Br J Surg* 2009;96:1015-22. [Crossref] [PubMed]
119. Kinoshita T, Sasako M, Sano T, et al. Phase II trial of S-1 for neoadjuvant chemotherapy against scirrhous gastric cancer (JCOG 0002). *Gastric Cancer* 2009;12:37-42. [Crossref] [PubMed]
120. Cheong JH, Hyung WJ, Chen J, et al. Surgical management and outcome of metachronous Krukenberg tumors from gastric cancer. *J Surg Oncol* 2004;87:39-45. [Crossref] [PubMed]
121. Yu P, Huang L, Cheng G, et al. Treatment strategy and prognostic factors for Krukenberg tumors of gastric origin: report of a 10-year single-center experience from China. *Oncotarget* 2017;8:82558-70. [PubMed]
122. Lu LC, Shao YY, Hsu CH, et al. Metastasectomy of Krukenberg tumors may be associated with survival benefits in patients with metastatic gastric cancer. *Anti-cancer Res* 2012;32:3397-401. [PubMed]
123. Yan D, Du Y, Dai G, et al. Management Of Synchronous Krukenberg Tumors From Gastric Cancer: a Single-center Experience. *J Cancer* 2018;9:4197-203. [Crossref] [PubMed]
124. Rosa F, Marrelli D, Morgagni P, et al. Krukenberg Tumors of Gastric Origin: The Rationale of Surgical Resection and Perioperative Treatments in a Multicenter Western Experience. *World J Surg* 2016;40:921-8. [Crossref] [PubMed]
125. Iijima Y, Akiyama H, Atari M, et al. Pulmonary Resection for Metastatic Gastric Cancer. *Ann Thorac Cardiovasc Surg* 2016;22:230-6. [Crossref] [PubMed]
126. Yoshida Y, Imakiire T, Yoneda S, et al. Ten cases of resected solitary pulmonary metastases arising from gastric cancer. *Asian Cardiovasc Thorac Ann* 2014;22:578-82. [Crossref] [PubMed]
127. Aurello P, Petrucciani N, Giulitti D, et al. Pulmonary metastases from gastric cancer: Is there any indication for lung metastasectomy? A systematic review. *Med Oncol* 2016;33:9. [Crossref] [PubMed]
128. Yang Y, Pei X, Yang M. Combination of apatinib and continuous nutritional support for a gastric cancer patient with brain metastasis prolongs survival. *J Clin Pharm Ther* 2018;43:726-9. [Crossref] [PubMed]
129. Ahn MJ, Lee K, Lee KH, et al. Combination of anti-PD-1 therapy and stereotactic radiosurgery for a gastric cancer patient with brain metastasis: a case report. *BMC Cancer* 2018;18:173. [Crossref] [PubMed]
130. Choi YJ, Kim DH, Han HS, et al. Long-term survival after gastrectomy and metastasectomy for gastric cancer with synchronous bone metastasis. *World J Gastroenterol* 2018;24:150-6. [Crossref] [PubMed]
131. Yoshida K, Yamaguchi K, Okumura N, et al. Is conver-

- sion therapy possible in stage IV gastric cancer: the proposal of new biological categories of classification. *Gastric Cancer* 2016;19:329-38. [Crossref] [PubMed]
132. Yamaguchi K, Yoshida K, Tanaka Y, et al. Conversion therapy for stage IV gastric cancer-the present and future. *Transl Gastroenterol Hepatol* 2016;1:50. [Crossref] [PubMed]
 133. Yamaguchi K, Yoshida K, Tanahashi T, et al. The long-term survival of stage IV gastric cancer patients with conversion therapy. *Gastric Cancer* 2018;21:315-23. [Crossref] [PubMed]
 134. Beom SH, Choi YY, Baek SE, et al. Multidisciplinary treatment for patients with stage IV gastric cancer: the role of conversion surgery following chemotherapy. *BMC Cancer* 2018;18:1116. [Crossref] [PubMed]
 135. Morgagni P, Solaini L, Framarini M, et al. Conversion surgery for gastric cancer: A cohort study from a western center. *Int J Surg* 2018;53:360-5. [Crossref] [PubMed]