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Review

Advanced gastric cancer: the value of surgery

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Summary. Gastric cancer is a common disease with high mortality. The definition of advanced gastric cancer is still debated. Radical surgery associated to appropriate systemic and intra-abdominal chemotherapy is the gold standard treatment. In presence of peritoneal carcinosis, reaching a complete cytoreduction is the key to achieve long-term survival. Adequate lymphadenectomy is also fundamental. Conversion therapy could be applied to selected IV stage patients. No definitive evidences exist regarding the oncological and surgical superiority of mini-invasive approaches over the classical open techniques. (www.actabiomedica.it)

Key words: advanced gastric cancer, chemotherapy, hipec, intraperitoneal, surgery, definition, metastasis, carcinosis

Introduction

Gastric cancer (GC) is the fifth cause of cancer death in the world. Some differences exist according to the geographic area. Eastern countries have a better prognosis in the treatment of these patients when compared to western. In Japan the survival for resectable GC is almost 70% (1), while in Europe and US the 5-year survival is almost 25% in advanced gastric cancer (AC) (2-6).

The TNM classification of the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) is widely used, even if with some criticisms (7-9).

However, precise definition of AC is still matter of debate. Some authors defined as AC the T3 and T4 cancers. As a counterpart, the vast majority considers advanced those tumors infiltrating beyond the submucosal layer that are not-early and not-metastatic even with N0 staging. Practically, AC could be considered the T2-T4b/N0-N3b/M0 according to the AJCC/UICC TNM classification. In addition the proposal of esophagogastric junction cancers classification to replace the Siewert one raised many concerns. Recently the new TNM 8th classification of neoplastic diseases redefined the classification of the gastric and gastroesophageal junction cancers (GEJC) and formally included the GEJC among the gastric cancers (10). A meta-analysis confirmed the same biological behavior of the GEJC and the AC. The main difference is the anatomical diffusion due to the localization, to the different anatomy of the two regions and the consequent lymphatic drainage (11).

Extension of gastric resection

Radical surgery including adequate resection and lymphadenectomy is the only curative treatment either for early stage either for advanced but non-metastatic disease. Lymphadenectomy could be considered adequate with the retrieval of at least 16 lymph nodes (12).

The recommended oncologically correct proximal margins are: at least 3 cm for T2 or higher degree tumors with "expansive growth pattern" and at least 5 cm in "infiltrative growth pattern" diseases. The concept of adequacy of surgical resection has been defined as total gastrectomy for large tumors or for tumors of the lesser curve and in general in all those situations in which resection margins cannot be respected.

Lymphadenectomy

Besides the penetration of the serosa, the principal factors strongly related with prognosis are the lymph node (LN) involvement (13) and the clearance of lymph nodes (14-16).

As a matter of fact lymphadenectomy is important in staging and in increasing the long-term survival (5, 13). Eastern and western countries use different standard to regulate the extension of the lymphadenectomy. In "standard lymphadenectomy" (D1) almost 15-18 lymph nodes (LN) must be removed to have a proper staging. In "extended lymphadenectomy" (over-D1) the number of LD to remove is 31-35 to have a better staging of the N3 (according to the TNM) and to increase survival (17-20). In D2 lymphadenectomy at least 27 LN should be retrieved for optimal results (19). In Europe, the state-of-the-art in curative-intent surgery for AC is gastrectomy, D2 lymphadenectomy and omentectomy (5, 13, 15, 21-23).

Extent of lymphadenectomies

- *D1 lymphadenectomy* includes the peri-gastric stations (from station 1 to 7) (5, 24). When facing esophageal-gastric junction tumors also the infradiaphragmatic, paraesophageal and supradiaphragmatic LN stations (19, 20, 110 and 111 LN stations) should be resected for D1 lymphadenectomy (5).
- *"D1 plus" lymphadenectomy* consists in the resection of the stations 8a, 9, and 11p too (25).
- *D2 lymphadenectomy* consists in the D1 resection associated to stations 10, 11d, and 12a (5, 25).
- *D3 lymphadenectomy* includes also the posterior (12p, 13, 14v) and para-aortic station (26).
- *Super-extender D3 lymphadenectomy* includes splenectomy or distal pancreatectomy associated to D2 lymphadenectomy.

At least 16 LN should be retrieved for accurate pathologic evaluation. Some data suggested no increase in accuracy of pN staging with an increase of LN retrieval (27).

D1 vs D2 vs D3 lymphadenectomy

In T1a tumor not suitable for endoscopic resection and for differentiated and ≤1.5 cm cT1bN0 lesions *D1 lymphadenectomy* is indicated (25). A *"D1 plus" lymphadenectomy* has been reported as an alternative of D2 in high-risk cT1N0. *D2 lymphadenectomy* is indicated for potentially curable T2–T4 tumors, as well cT1N + tumors (25). Two randomized controlled trials (RCTs) (18, 28, 29) reported a superiority of the D1 compared with D2 lymphadenectomy. However, no other studies confirmed these results (22, 23, 30). The Italian Gastric Cancer Study Group (GIRCG) showed that D2 dissection without splenectomy and pancreatic resection is feasible and safe with similar results to D1 (22). Some data from a randomized trial (18, 31) showed an increased survival rate in patients who underwent D2 vs. D1, where gastric-cancer-related death and a regional recurrence were higher in D1. Another RCT (25) comparing the difference between D1 plus and D2 showed higher LN removal in D2 lymphadenectomy, no differences in LN ratio, no significant differences in median recurrence rate.

D3 lymphadenectomy is supposed to provide a better local control of disease in advanced gastric tumors with mixed-diffuse histotype (32). As in upper third GC 29% of para-aortic LN are involved compared to the 7% of middle and lower third GC ($p<0.001$), the inclusion of para-aortic LN stations (16a, 16b) is important in upper third tumors, in larger tumors, or in tumor with station 7 involvement (33, 34). No benefit in survival rate is related to routine extended lymphadenectomy and removal of para-aortic LN (35, 36).

Super-extender D3 lymphadenectomy is strongly not recommended and is in the most of cases not necessary (13, 16, 37-39). Even in scenarios of higher risk for splenic hilum node involvement, i.e., with proximal and mid greater curvature primaries, spleen-preserving hilum lymphadenectomy can be performed with satis-

factory results (40). Splenectomy and pancreatectomy might be considered beneficial only in case the primary tumor or the LN metastasis involve these organs (16, 39).

The evaluation of the possible role of an extended lymphadenectomy in reducing the risk of a local recurrence has been reported in several studies (32, 34, 41-43).

Patients who underwent a D2 with para-aortic LN dissection (PAND) presented better outcome in terms of mortality and morbidity, compared to the only D2 have been reported (21). However, another study (34) reported that D2 with PAND has no improving in survival or recurrence rate in T2-subserosa, T3, T4 stages with similar perioperative mortality and an increase in morbidity for the D2 PAND group.

Wu et al. found in a RCT (41) evaluating D1 vs. D3 that morbidity rate was higher in D3 and overall survival was significantly higher and regional recurrence rate lower in D3 (35). De Manzoni reported a higher recurrence rate in D3 group in case of intestinal pattern then in mixed/diffuse pattern with a similar mortality thus emphasizing the necessity to tailor lymphadenectomy to the histology (32).

Cytoreductive surgery

In the event of local or diffuse peritoneal carcinosis (PC) the best approach combines systemic chemotherapy, radical surgery and intra-peritoneal chemotherapy (IPC). This multimodal treatment radically changed the outcomes (44-48).

Differently from ovarian cancer as well as for other diseases (49, 50) in GC with PC, cytoreductive surgery (CRS) alone is not accompanied by survival benefits. As showed by Yamamura et al. CRS alone cannot be effective in treating PC because of invisible cancer cells remain even after surgical procedure. As a counterpart, CRS plus peri-operative chemotherapy is feasible and safe with a significant increase in survival rate in GC with PC (51-54). Furthermore, a meta-analysis clearly showed a survival benefit in patients affected by advanced GC, with or without PC, treated with IPC (44). An independent favourable prognostic factor during CRS if associated to IPC is the completeness of cytoreduction (52, 55-57). A recent meta-analysis reported an increase in 1, 2, 3, and 5-years survival rate in CC-0/CC-1 cytoreduction (58) and CC-0 showed better outcomes than CC-1 with an increased survival at 1 and 3 years. The Peritoneal Cancer Index (PCI) evaluation is mandatory in selecting patients for CRS+IPC treatment. Yonemura et al. showed that it was possible to obtain a complete cytoreduction in 91% of cases in presence of a PCI≤6 but only in 42% with a PCI≥7. Moreover, the survival rate in PCI score ≤6 was significantly better than in PCI score ≥7 (45). Survival rates at different time points change significantly above and below a PCI of 12 with a progressive decrease for higher PCI scores (57, 59-61.

Surgery for IV stage gastric cancer

Chemotherapy remains the main therapeutic approach for stage IV GC and surgery is usually confined to a palliative resection or by-pass operation to relieve symptoms. However, the median survival time of this cohort of patients remains to be around 13-16 months (62). Furthermore, the REGATTA trial demonstrated that the initial removal of the primary tumor in stage IV GC could be beneficial just in case of only one affected organ other than the site of primary tumor (63).

Stage IV GC patients are heterogeneous and could be divided into four categories (62) (64):

- Category 1: absence of macroscopic PC and potentially resectable metastases
- Category 2: absence of macroscopic PC and marginally resectable metastases
- Category 3: presence of macroscopic PC without other distant metastases
- Category 4: presence of macroscopic PC and other organ metastases.

According to recent studies, patients in category 1 could be eligible for neoadjuvant chemotherapy and subsequent gastrectomy plus metastasectomy. For the other categories, much attention is being paid to conversion therapy. It is defined as a surgical treatment aiming at an R0 resection after chemotherapy for tumors that were originally unresectable for technical or oncological reasons (64). In a study on 259 patients with IV stage GC, planned resection after neoadjuvant chemotherapy was performed in 7 patients and con-

version surgery in 77. Although only 51,2% of patients underwent R0 resection, median survival time was 41.3 months, that is much longer than that reported from the first-line chemotherapy trials (62). Metastasectomy along with resection of the primary tumor might be feasible for this population, once the metastases have responded well to the chemotherapy. Some authors recommend the surgical treatment of hepatic metastases from gastric cancer to be taken into consideration after careful evaluation of each single case, as only a radical approach with curative intent is worthy (65).

Mini-invasive surgical approach

Although studies about mini-invasive surgical approach mixed AC and early gastric cancer patients exist, no dedicated studies to AC were conducted. Results however suggest the possibility to apply the mini-invasive approach to AC without PC.

Laparoscopic surgery

In early gastric cancer laparoscopic resections associated to D1 lymphadenectomy obtained better results than open technique in terms of postoperative pain, time to return to normal bowel function and resumption of oral feeding, time to recovery, length of hospital stay, cosmetic results and financial outcome (66-69). Morbidity and mortality rates in laparoscopy are not statistically different to open resections (29) (22, 70). The role of laparoscopy in D2 or higher for lymphadenectomy is still matter of debate. According to some authors, laparoscopy reduces the accuracy in dissecting lymph nodes, especially from high risk nodal stations. Wang et al. in a meta-analysis including 17 trials (2313 patients) comparing laparoscopic and open total gastrectomy (71) demonstrated a longer operative time, earlier hospital discharge, earlier passage of flatus, quicker resumption of oral intake, fewer analgesic uses, and reduced postoperative morbidity in laparoscopic approach. No difference was found in terms of hospital mortality, resected lymph nodes, proximal resection margin and 5-year overall and disease-free survival. Another meta-analysis of 15 non-randomized trails substantially confirmed the outcomes (72).

Robotic surgery

No sufficient data exist about feasibility, safety and eventual advantages of robotic gastrectomy compared to open or laparoscopic gastrectomy in early gastric cancer neither in AC. No reports exist about the use of robotic gastrectomy in patients with AC and PC.

Liao et al. published a meta-analysis of 4 studies (5780 patients) comparing robotic and open gastrectomy. Longer operation time, lower blood loss and shorter hospital stay were associated to robotic gastrectomy. Overall morbidity and number of resected lymph nodes were not different (73).

Conclusions

Therapeutic approach of AC is based on radical surgery with adequate lymphadenectomy, associated to appropriate systemic and intra-abdominal chemotherapy. In presence of PC reaching a complete removal of visible disease is even more important. In stage IV GC conversion therapy could be considered in selected patients with good response to chemotherapy. No definitive evidences exist regarding the oncological and surgical superiority of the mini-invasive approach over the classical open technique.

References

1. World Health Organization. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide. 2012.
2. Karimi P, Islami F, Anandasabapathy S, Freedman ND, Kamangar F. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. Cancer Epidemiol Biomarkers Prev 2014; 23: 700-713 [PMID: 24618998 DOI: 10.1158/1055-9965].
3. Bauer K, Schroeder M, Porzsolt F, Henne-Bruns D. Comparison of international guidelines on the accompanying therapy for advanced gastric cancer: reasons for the differences. J Gastric Cancer 2015 Mar; 15(1): 10-8.
4. Wang J, Sun Y, Bertagnolli MM. Comparison of Gastric Cancer Survival Between Caucasian and Asian Patients Treated in the United States: Results from the Surveillance Epidemiology and End Results (SEER) Database. Ann Surg Oncol 2015 Jan 29.
5. Japanese Gastric Cancer Association. Japanese Classification

of Gastric Carcinoma – 3nd English Edition. Gastric Cancer 2011 Jun; 14(2): 101-12.
6. Verlato G, Giacopuzzi S, Bencivenga M, Morgagni P, De Manzoni G. Problems faced by evidence-based medicine in evaluating lymphadenectomy for gastric cancer. World J Gastroenterol 2014 Sep 28; 20(36): 12883-91.
7. Washington K. 7th edition of the AJCC cancer staging manual: stomach. Ann Surg Oncol 2010; 17: 3077-3079 [PMID: 20882416 DOI: 10.1245/s10434-010-1362-z].
8. Sobin LH, Gospodarowicz MK, Wittekind C. International Union Against Cancer (UICC) TNM Classification of Malignant Tumors. 7th ed. New York: Wiley-Liss; 2010.
9. Qiu MZ, Wang ZQ, Zhang DS, Liu Q, Luo HY, Zhou ZW, Li YH, Jiang WQ, Xu RH. Comparison of 6th and 7th AJCC TNM staging classification for carcinoma of the stomach in China. Ann Surg Oncol 2011; 18: 1869-1876.
10. Ajani JA, In H, Sano T, et al.,Stomach, Amin MB E. AJCC Cancer Staging Manual, eighth ed. 2017.
11. Coccolini F, Nardi M, Montori G, Ceresoli M, Celotti A, Cascinu S, Fugazzola P, Tomasoni M, Glehen O, Catena F, Yonemura Y, Ansaloni L. Neoadjuvant chemotherapy in advanced gastric and esophago-gastric cancer. Meta-analysis of randomized trials. Int J Surg 2018 Mar; 51: 120-127. doi: 10.1016/j.ijsu.2018.01.008. Epub 2018 Feb 20. Review.
12. Seevaratnam R, Bocicariu A, Cardoso R, Yohanathan L, Dixon M, Law C, Helyer L, Coburn NG. How many lymph nodes should be assessed in patients with gastric cancer? A systematic review. Gastric Cancer 2012; 15: S70-88.
13. McCulloch P1, Niita ME, Kazi H, Gama-Rodrigues JJ. Gastrectomy with extended lymphadenectomy for primary treatment of gastric cancer. Br J Surg 2005 Jan; 92(1): 5-13.
14. Deng J, Zhang R, Pan Y, Wang B, Wu L, Jiao X, Bao T, Hao X, Liang H. Comparison of the staging of regional lymph nodes using the sixth and seventh editions of the tumor-node-metastasis (TNM) classification system for the evaluation of overall survival in gastric cancer patients. Surgery 2014 Jul: 156(1): 64-74.
15. Schwarz RE. Current status of management of malignant disease: current management of gastric cancer. J Gastrointest Surg 2015 Apr; 19(4): 782-8.
16. Jiang L, Yang KH, Chen Y, Guan QL, Zhao P, Tian JH, Wang Q. Systematic review and meta-analysis of the effectiveness and safety of extended lymphadenectomy in patients with resectable gastric cancer. Br J Surg 2014 May; 101(6): 595-604.
17. Siewert JR, Bottcher K, Roder JD et al. Prognostic relevance of systematic lymph node dissection in gastric carcinoma. Br J Surg 1993; 80: 1015-1018.
18. Bonenkamp JJ, Hermans J, Sasako M, van de Velde CJH, for the Dutch Gastric Cancer Group. Extended lymph-node dissection for gastric cancer. N Engl J Med 1999; 340(12): 908-14.
19. Wagner PK, Ramaswamy A, Rueschoff J et al. Lymph node count in the upper abdomen: anatomical basis for lymphadenectomy in gastric cancer. Br J Surg 1991; 78:825-827.
20. Bozzetti F. Principles of surgical radicality in the treatment of gastric cancer. Extended lymph-node dissection for gastric cancer. N Engl J Med 1999 Mar 25; 340(12): 908-14. Surg Oncol N Am 2001; 10:833-854.
21. Kulig J, Popiela T, Kolodziejczyk P, Sierzega M, Szczepanik A and Group., Polish Gastric Cancer Study. Standard D2 versus extended D2 (D2+) lymphadenectomy for gastric cancer: an interim safety analysis of a multicenter, randomized, clinical trial. Am J Surg 2007 Jan; 193(1): 10-5.
22. Degiuli M, Sasako M, Ponti A, Soldati T, Danese F, Calvo F. Morbidity and mortality after D2 gastrectomy for gastric cancer: results of the Italian Gastric Cancer Study Group prospective multicenter surgical study. Clin Oncol 1998 Apr; 16(4): 1490-3.
23. Degiuli M, Sasako M, Ponti A, Calvo F. Survival results of a multicentre phase II study to evaluate D2 gastrectomy for gastric cancer. Br J Cancer 2004 May 4; 90(9): 1727-32.
24. Song W, He Y, Wang S, He W, Xu J. Significance of the lymph nodes in the 7th station in rational dissection for metastasis of distal gastric cancer with different T categories. Chin J Cancer Res 2014 Aug; 26(4): 423-30.
25. Galizia G, Lieto E, De Vita F, Castellano P, Ferraraccio F, Zamboli A, Mabilia A, Auricchio A, De Sena G, De Stefano L, Cardella F, Barbarisi A, Orditura M. Modified versus standard D2 lymphadenectomy in total gastrectomy for nonjunctional gastric carcinoma with lymph nodes metastases. Srgery 2015 Feb; 157(2): 285-96.
26. Lee J, Lim do H, 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: 268-273.
27. De Manzoni G, Verlato G, Roviello F, Morgagni P, Di Leo A, Saragoni L, Marrelli D, Kurihara H, Pasini F. The new TNM classification of lymph node metastasis minimises stage migration problems in gastric cancer patients. Br J Cancer 2002 Jul 15; 87(2): 171-4.
28. Cuschieri A, Weeden S, Fielding J, Bancewicz J, Craven J, Joypaul V, Sydes M, Fayers P. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. Br J Cancer 1999; 79(9-10): 1522-30.
29. Cuschieri A, Fayers P, Fielding J, Craven J, Bancewicz J, Joypaul V, Cook P. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. Lancet 1996 Apr 13; 347(9007): 995-9.
30. McCulloch P, Nita ME, Kazi H, Gama-Rodrigues J. Extended versus limited lymph nodes dissection technique for adenocarcinoma of the stomach. Cochrane Database Syst Rev. 2004 Oct 18; (4):CD001964.
31. Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol 2010; 11: 439-49.
32. De Manzoni G, Verlato G, Bencivenga M, Marrelli D, Di Leo A, Giacopuzzi S, Cipollari C, Roviello F. Impact of

super-extended lymphadenectomy on relapse in advanced gastric cancer. Eur J Surg Oncol 2015 Apr; 41(4): 534-40.
33. Roviello F, Pedrazzani C, Marrelli D, Di Leo A, Caruso S, Giacopuzzi S, Corso G, de Manzoni G. Super-extended (D3) lymphadenectomy in advanced gastric cancer. Eur J Surg Oncol 2010 May; 36(5): 439-46.
34. Sasako M, Sano T, Yamamoto S, Kurokawa Y, Nashimoto A, Kurita A, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. N Engl J Med 2008; 359: 453-62.
35. Wu CW, Hsiung CA, Lo SS, et al. Nodal dissection for patients with gastric cancer: a randomised controlled trial. Lancet Oncol 2006; 7: 309-15.
36. Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol 2010; 11: 439-49.
37. Schwarz RE, Karpeh MS, Brennan MF. Surgical management of gastric cancer: the Western experience. In: Daly JM, Hennessy TPJ, Reynolds JV, eds. Management of upper gastrointestinal cancer. London: W.B. Saunders; 1999: 83-106.
38. Kodera Y, Schwarz RE, Nakao A. Extended lymph node dissection in gastric carcinoma: where do we stand after the Dutch and British randomized trials? . J Am Coll Surg 2002; 195: 855-64.
39. Kuo CY, Chao Y, Li CP. Update on treatment of gastric cancer. J Chin Med Assoc. 2014 Jul;77(7):345-53.
40. RE., Schwarz. Spleen-preserving splenic hilar lymphadenectomy at the time of gastrectomy for cancer: Technical feasibility and early results. J Surg Oncol 2002; 79: 73-6.
41. Wu CW, Hsiung CA, Lo SS, Hsieh MC, Shia LT, Whang-Peng J. Randomized clinical trial of morbidity after D1 and D3 surgery for gastric cancer. Br J Surg 2004 Mar; 91(3): 283-7.
42. Wu CW, Hsiung CA, Lo SS, Hsieh MC, Chen JH, Li AF, Lui WY, Whang-Peng J. Nodal dissection for patients with gastric cancer: a randomised controlled trial. Lancet Oncol 2006 Apr; 7(4): 309-15.
43. Sano T, Sasako M, Yamamoto S, Nashimoto A, Kurita A, Hiratsuka M, Tsujinaka T, Kinoshita T, Arai K, Yamamura Y, Okajima K. Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended paraortic lymphadenectomy-Japan Clinical Oncology group Study 9501. J Clinical Oncol 2004 Jul 15; 22(14): 2767-73.
44. Coccolini F, Cotte E, Glehen O, Lotti M, Poiasina E, Catena F, Yonemura Y, Ansaloni L. Intraperitoneal chemotherapy in advanced gastric cancer. Meta-analysis of randomized trials. Eur J Surg Oncol 2014 Jan; 40(1): 12-26.
45. Yonemura Y, Elnemr A, Endou Y, et al. Multidisciplinary therapy for treatment of patients with peritoneal carcinomatosis from gastric cancer. World J Gastrointetinal Oncol 2010; 2: 85-97.
46. Montori G, Coccolini F, Ceresoli M, Catena F, Colaianni N, Poletti E, Ansaloni L. The treatment of peritoneal carcinomatosis in advanced gastric cancer: state of the art. Int J Surg Oncol 2014; 2014: 912418.
47. 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 Sep; 110(3): 275-84.
48. Fugazzola P, Coccolini F, Montori G, Ceresoli M, Baggi P, Costanzo A, Tomasoni M, Gregis F, Nozza S, Ansaloni L. Overall and disease-free survival in patients treated with CRS + HIPEC with cisplatin and paclitaxel for gastric cancer with peritoneal carcinomatosis. J Gastrointest Oncol 2017 Jun; 8(3): 572-582. doi: 10.21037/jgo.2017.03.11.
49. Coccolini F, Gheza F, Lotti M, Virzì S, Iusco D, Ghermandi C, Melotti R, Baiocchi G, Giulini SM, Ansaloni L, Catena F. Peritoneal carcinomatosis. World J Gastroenterol 2013 Nov 7;19(41):6979-94. World J Gastroenterol 2013 Nov 7; 19(41): 6979-94.
50. Bristow RE, Chi DS. Platinum-based neoadjuvant chemotherapy and interval surgical cytoreduction for advanced ovarian cancer: a meta-analysis. Gynecol Oncol 2006 Dec; 103(3): 1070-6. Epub 2006 Jul 27.
51. Coccolini F, Campanati L, Catena F, Ceni V, Ceresoli M, Jimenez Cruz J, Lotti M, Magnone S, Napoli J, Rossetti D, De Iaco P, Frigerio L, Pinna A, Runnebaum I, Ansaloni L. Hyperthermic intraperitoneal chemotherapy with cisplatin and paclitaxel in advanced ovarian cancer: a multicenter prospective observational study. J Gynecol Oncol 2015 Jan; 26(1): 54-61. doi: 10.3802/jgo.2015.26.1.54. Epub 2014 Nov 3.
52. Yonemura Y, Shinbo M, Hagiwara A, et al. Treatment for potentially curable gastric cancer patients with intraperitoneal free cancer cells. Gastroenterological Surg 2008; 31: 802-12. [in Japanese].
53. Yonemura Y, Bandou E, Sawa T, et al. Neoadjuvant treatment of gastric cancer with peritoneal dissemination. EJSO 2006; 32: 661-5.
54. Glehen O, Gilly FN, Arvieux C, Cotte E, Boutitie F, Mansvelt B, Bereder JM, Lorimier G, Quenet F, Elias D and Chirurgie. Association Française de. 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 Sep; 17(9): 2370-7. doi: 10.1245/s10434-010-1039-7. Epub 2010 Mar 25.
55. 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.
56. Yonemura Y, Kawamura T, Bandou E, et al. Treatment of peritoneal dissemination from gastric cancer by peritonectomy and chemohyperthermic peritoneal perfusion. Brit J Surg 2005; 92: 370-5.
57. Glehen O, Gilly FN, Boutitie F, Bereder JM, Quenet F, Sideris L, Mansvelt B, Lorimier G, Msika S, Elias D and Association., French Surgical. Toward curative treatment of

peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1,290 patients. Cancer 2010 Dec 15; 116(24): 5608-18. doi: 10.1002/cncr.25356. Epub 2010 Aug 24.
58. Coccolini F, Catena F, Glehen O, Yonemura Y, Sugarbaker PH, Piso P, Montori G, Ansaloni L. Complete versus incomplete cytoreduction in peritoneal carcinosis from gastric cancer, with consideration to PCI cut-off. Systematic review and meta-analysis. Eur J Surg Oncol 2015 april 14.
59. Scaringi S, Kianmanesh R, Sabate JM, Facchiano E, Jouet P, Coffin B, Parmentier G, Hay JM, Flamant Y, Msika S. Advanced gastric cancer with or without peritoneal carcinomatosis treated with hyperthermic intraperitoneal chemotherapy: a single western center experience. Eur J Surg Oncol 2008 Nov; 34(11): 1246-52. doi: 10.1016/j.ejso.2007.12.003. Epub 2008 Jan 28.
60. 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 May 1; 101(6): 457-64.
61. Yang XJ, Huang CQ, Suo T, Mei LJ, Yang GL, Cheng FL, Zhou YF, Xiong B, Yonemura Y, Li Y. 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 Jun; 18(6): 1575-81. doi: 10.1245/s10434-011-1631-5. Epub 2011 Mar 23.
62. Yamaguchi K, Yoshida K, Tanahashi T, Takahashi T, Matsuhashi N, Tanaka Y, Tanabe K, Ohdan H. The long-term survival of stage IV gastric cancer patients with conversion therapy. Gastric cancer 2018; 21: 315-323.
63. Fujitani Kazumasa, Yang Han-Kwang, Mizusawa Junki, Kim Young-Woo, Terashima Masanori, 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.
64. Yoshida K, Yamaguchi K, Okumura N, Tanahashi T, Kodera Y. Is conversion theraphy possible in stage IV gastriccancer: the proposal of new biological categories of classification. Gastric Cancer 2016; 19: 329-338. DOI 10.1007/s10120-015-0575-z.
65. Ministrini S, Solaini L, Cipollari C, Sofia S, Marino E, D'Ignazio A, Bencivenga M, Tiberio GAM. Surgical treatment of hepatic metastases from gastric cancer. Updates in Surgery 2018; 70: 273-278. https://doi.org/10.1007/s13304-018-0536-2.
66. Kitano S, Shiraishi N, Fujii K, Yasuda K, Inomata M, Adachi Y. A randomized controlled trial comparing open vs laparoscopy-assisted distal gastrectomy for the treatment of early gastric cancer: an interim report. Surgery 2002; 131: S306-S311.
67. Lee JH, Han HS, Lee JH. A prospective randomized study comparing open vs laparoscopy-assisted distal gastrectomy in early gastric cancer: early results. Surg Endosc 2005; 19: 168-173 .
68. Kim HH, Hyung WJ, Cho GS, Kim MC, Han SU, Kim W, Ryu SW, Lee HJ, Song KY. Morbidity and mortality of laparoscopic gastrectomy versus open gastrectomy for gastric cancer: an interim report--a phase III multicenter, prospective, randomized Trial (KLASS Trial). Ann Surg 2010 Mar; 251(3): 417-20. doi: 10.1097/SLA.0b013e3181cc8f6b.
69. Yasunaga H, Horiguchi H, Kuwabara K, Matsuda S, Fushimi K, Hashimoto H, Ayanian JZ. Outcomes after laparoscopic or open distal gastrectomy for early-stage gastric cancer: a propensity-matched analysis. Ann Surg 2013; 257: 640-646 .
70. Bonenkamp JJ, Songun I, Hermans J, Sasako M, Welvaart K, Plukker JT, van Elk P, Obertop H, Gouma DJ, Taat CW. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. Lancet 1995; 345: 745-748 .
71. Wang W, Zhang X, Shen C, Zhi X, Wang B, et al. Laparoscopic versus Open Total Gastrectomy for Gastric Cancer: An Updated Meta-Analysis. PLoS ONE 2014; 9(2): e88753.
72. Xiong JJ, Nunes QM, Huang W, Tan CL, Ke NW, Xie SM, Ran X, Zhang H, Chen YH, Liu XB. Laparoscopic vs open total gastrectomy for gastric cancer: A meta-analysis. World J Gastroenterol 2013; 19(44): 8114-8132.
73. Liao G, Chen J, Ren C, Li R, Du S, Xie G, Deng H, Yang K, Yuan Y. Robotic versus Open Gastrectomy for Gastric Cancer: A Meta-Analysis. PLoS ONE 2013; 8(12): e81946.

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