Treatment of advanced gastric cancer

Gastrectomy with D2 lymphadenectomy: a review

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Radical gastrectomy with regional lymphadenectomy is the mainstay of curative treatment for advanced gastric cancer that has penetrated the submucosa: the depth of invasion (i.e extension into the muscularis propria) has been used to divide gastric carcinoma in early and advanced stages (1).

The procedure can be undertaken in the context of total or subtotal gastrectomy where D2 lymphadenectomy indicates nodal dissection to the N2 level.

This has been the standard treatment for advanced gastric carcinoma in Japan since the sixties (2, 3, 4, and 5).

The majority of patients in the western countries, in South America, in Africa, in Middle East present advanced stages and the majority of patients who undergo gastrectomy are found to have metastatic nodal involvement (6In the meantime, advanced but still curable gastric cancer is associated with very high recurrence rates, even after R0 gastrectomy (7).

Although the regional lymphadenectomy has been described five decades ago (8) and widely practiced in Asian and some western institutions with remarkable results, it still remains controversed in this setting.

At first, the definition of D2, which is here the subject of our report, is not clearly defined in the asian or western authors: it is "standard" in these and "extended" in those.

The rationale in favor of D2 lymphadenectomy includes:

- a better regional disease control
- a more appropriate pathologic staging
- an overall improved survival
- with a relapse free survival

- with acceptable hospital mortality
- Without excessive operative morbidity and finally an acceptable quality of life.

To realize these objectives, a rigorous pre-operative staging is mandatory: all classifications find use for TNM: T for tumor, N for lymph node and M for metastasis.

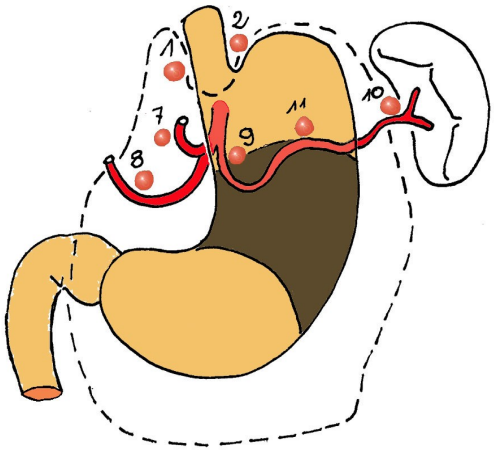
To evaluate these parameters, we have:

- endoscopy and biopsy
- imaging techniques such CT scan or RMI
- ultrasound endoscopy
- Pet scan wich evaluate more or less accurately T and M but fails to give an idea about the lymph node status (N).

  For T, we have location, size, depth, and histology which indicate total or subtotal gastrectomy if there is no metastases (M0).

The type of resection, total or subtotal, is selected according to the location of the tumor: if the proximal margin of the tumor is proximal to the line between DEMEL's point on the greater curvature and the point 5cm below the cardia on the lesser curvature, total gastrectomy is indicated.

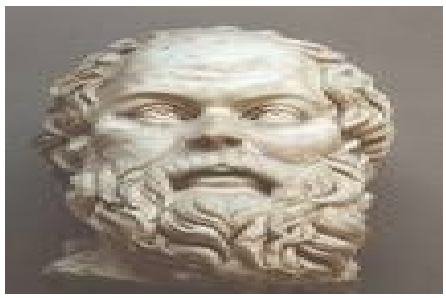
Furthermore, a total gastrectomy is required irrespective of the tumor, in cases of BORREMANN type 4 cancer or if there is obvious lymph node metastasis at the right cardial region; otherwise, a distal subtotal gastrectomy is performed (9.10)



What kind of lymphadenectomy?

" Surgery of malignant disease is not the surgery of organs, it is an

anatomy of the lymphatic system" Moyhann said.



Some authors agree with the philosophy and the concept of extended lymph nose dissection was developed five decades ago, and there are claims based on historical data that the extended surgical resection, especially extended lymph node dissection, improves the outcome in gastric cancer (2, 3, 5) with results challenging every competition.

Numerous Japanese publications report about hundred and hundred gastrectomies an average of mortality less than 1%, an acceptable morbidity of 20% and an overall five years survival of 50 to 70%!

For instance, SANO et al (11) reported in 2002 one thousand consecutive gastrectomies without operative mortality!

Such results led to a western reaction: the opponents to the Moyham's philosophy in western countries claimed that:

- Japanese authors are confirmed liars (12)

- Japanese are thinner than western patients:

that's not always true (13) but a medical report (14) and a recent Japanese randomized trial

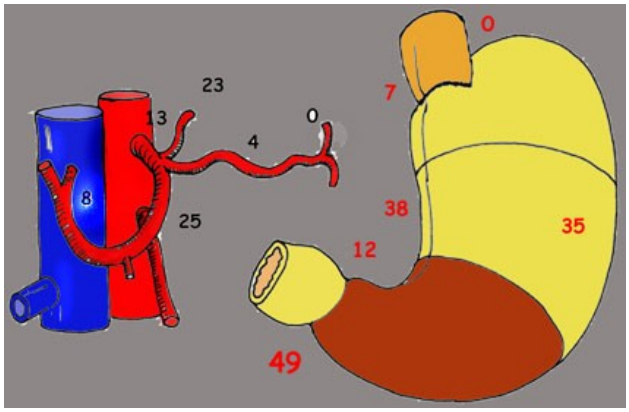
(15) confirm effectively that Body Mass Index is a prognostic factor for the success of lymph node dissection and predicts the outcome of gastric carcinoma patients.

- Japanese patients are younger: it is true and Nishi (16) found in

  Japan an average of 10 years less that of western countries.

- The gastric carcinomas are more frequently located in the distal third than in the proximal third in the Japanese patients in opposition at that observed in western countries: surgery would than be easier in these cases.

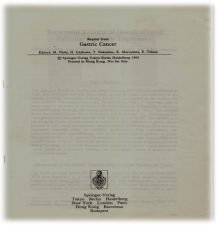
It is true for the location (17) but we have to emphasize that there is no meaningful difference between total or subtotal gastrectomy with regard to prognostic factor (18).



- Japanese gastric carcinoma would be biologically different, less aggressive than in Western countries (19, 20, 21)
- This stingy hypothesis merit no comments.
- Earlier cancer, with better prognosis, are more frequent in Japan: it is true

  and we have only to congratulate Japanese doctors for these good results scheduled in a serious health program.

- Japanese reports are retrospective and then, the are not scientifically valid: according to the recent movement of "evidence based medicine" (22) randomized clinical trials (RCTs) are the best methods of effectiveness and appropriateness of treatment.



So the European opponents performed two RCTs (23, 34) which were conducted following the criteria and the procedure established by the Japanese and comparing D1 versus D2.

The Dutch trial gathered 771 patients operated on in 80 institutions over 4 years: the morbidity rate was high (4% for D1 and 10% for D2); so was the morbidity rate (25% for D1 and 43 for D2). There were no significant difference for the 5 years survival between D1 (45%) and D2 (43%).

The Medical Research Council (400 patients) showed the same results (24).

The conclusion of these two RCTs does not support the routine use of D2 lymph node dissection in patients with gastric cancer. In the mean time, in Japan, D1 lymphadenectomy dissections are listed as palliative procedure and then a RCT D1 versus D2 would be considered as unethical.

More over, the two European trials are:

- multicenter studies with too much hospitals and surgeons concerned
- these surgeons are often unfamiliar with the Japanese procedure: even they had a Japanese supervisor, one could not learn a new technique in a book or in a videotape. Some of these surgeons performed only 2 gastrectomies/ year! (25).

<u>There is also a quality control problem:</u>

It is true that "by working with the Japanese expert at the operation table, many surgeons, including all the regional consulting surgeons, were able to learn the new surgical skills in the best way to teach a meticulous or complicated technique with which most surgeons were previously unfamiliar, and is far more instructive than reading about or watching" (1).

Despite these respectable speeches, we have to deplore 51% of protocol violation in the Dutch trial! (23).

So, this failure is linked to the inexperience of the participating surgeons of the trials.

Their respective learning curve is far from the Japanese or the Asian in general. For instance, in a recent Korean trial (26), 2 juniors staff surgeons had completed a two fellowship course on gastric cancer surgery in university hospital: during this period each surgeon initially performed gastric cancer surgeries as an assistant for more than 200 annually.

Surgeon A performed 102, while surgeon B performed 96 total gastric resection with D2 lymphadenectomy.

The learning period for total gastrectomy with D2 lymph node dissection for these two juniors members of staff was calculated as 23-35 cases, presuming a 92.5% success rate (i.e reviewed lymph node number cut off value required for satisfactory D2 lymph node dissection was defined as > 25).

It was observed no death and 25 complications for the 198 patients (12.6%). When we compare with the European RCTs, the difference is overwhelming.

In the Mc Donald's recent chemoradiation trial (27), more than 54% had D0 resection and only 10% a D2 resection!

In the dutch trial, the proportion of non compliance (patients who did not complete D2 lymph node dissection) was 51%.

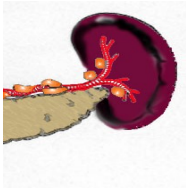
Conversely, the contamination (dissection of lymph node outside the indicated area) blurring thereby the distinction between the two procedure being compared.

The number of reviewed lymph nodes reflects the performance of an institution and its surgeons and pathologists: thus, the pathologist learning curve should be considered together with that of surgeons.

So, quality control is one of the most important factor in both surgical and clinical trials for patients who undergo surgery (1, 28).

Moreover, in the british and dutch trials (23, 24), splenectomy with or without distal pancreatectomy was highlighted as a major risk factor for operative morbidity and mortality.

Cushieri et al's evaluation of the 100 patients randomized to a D1 or D2 lymphadenectomy found a significant survival difference between patients with gastrectomy alone compared with to those with gastrectomy and splenectomy or pancreatosplenectomy, regardless of the extent of lymphadenectomy.



Splenectomy for the purpose of lymph node dissection should not be mandatory, and surgeons should consider spleen preservation in gastric cancer patients who have no definite splenic hilar lymph node enlargement or any direct invasion of the spleen.

Taking into account these recommandations (essentially sparing spleen and pancreas/gastrectomy with D2 lymph node dissection) is a safe procedure and actually numerous western single institutions have adopted these procedure, sometimes reported in non randomized studies (29, 33) or in a randomized clinical trials (34).

The incidence of complications observed in centers specializing in this surgical procedure has proven to be low: generally it is only slightly higher than reported by Japanese authors.

The first Japanese RCT initiated by Takeshi Sano and colleagues compared D2 versus D3 lymphadenectomy (35). One of their conclusion is that D2 lymph node dissection is safe and worthwhile.

Moreover, the late results of the Dutch trial (36) are less dismal than previously and the results suggest a better survival after D2 lymph node dissection in N2 patients: that should be a good idea to stratify the patients in controlled trials because the best way to eliminate stage migration is by comparing long term survival among all patients who had a D1 or D2 dissection with curative intent.

Precisely, the opponents of D2 lymph node dissection argue that this one improve the staging and not the survival. The consequence the so called "Will Rogers phenomenon" in which stage migration may improve stage specific survival regardless of a real survival benefit (37).

Concerning classification, there are 2 main classifications:

- the current main classification systems for gastric cancer are the sixth edition of the UICC/TNM classification (2002 – 38)
- and the thirteenth edition of the Japanese classification of gastric carcinoma (second English classification 1998 – 39).

Staging has a variety of purposes:

- indication of prognosis
- ideally it should be able to provide a framework from treatment decision

- and also it should allow evaluation of the treatment with meaningful comparisons between different treatments.

The UIUC/TNM staging system divides N stage on the basis of number of metastatic nodes, while the Japanese classification stresses the location of invaded nodes.

The UIUC and AJCC reached complete agreement that the cut off points for the N classification should be as follow:

PN1: 1-6 involved regional lymph nodes

PN2: 7-15 involved regional lymph nodes

PN3: more than 15 involved regional lymph nodes.

A minimum of 15 lymph nodes should be examined to determine whether a patient is N0.

TNM classification, 5th edition; 1997

		M0				M1
		N0	N1	N2	N3	
M0	T1	IA	IB	II		
	T2	IB	II	IIIA		
	T3	II	IIIA	IIIB		
	T4	IIIA			IV	
M1						

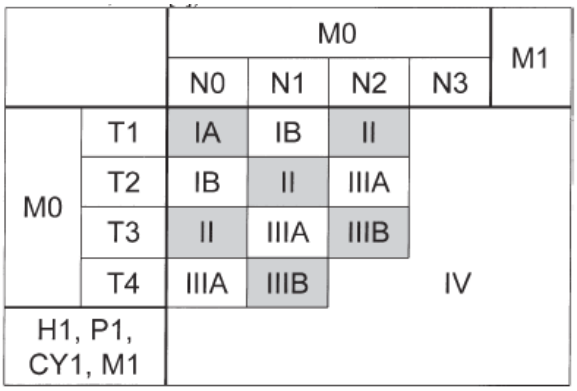
N1, 1–6 involved nodes; N2, 7–15 involved nodes; N3, >15 nodes

N1, 1–6 involved nodes; N2, 7–15 involved nodes; N3, _15 nodes

The Japanese gastric classification: in its 13th edition, the general rules changed from the S stage to the T stage system, which was equivalent to the T staging of the UICC system. The JCGA gives a number to all of regional lymphnode station (1 to 16), which are classified in 3 tiers according to the location of the primary tumor. These stations are further classified into $N_1/N_2/N_3$ according to the location of the primary tumor. There were a variety of changes in this classification such as rules of

endoscopic mucosal resection (EMR) and for staging carcinoma of the remnant stomach, and peritoneal cytology has been included in staging (40).

Japanese classification, 13th edition; 1999 (2nd English edition; 1998)



		M0				M1
		N0	N1	N2	N3	
M0	T1	IA	IB	II		
	T2	IB	II	IIIA		
	T3	II	IIIA	IIIB		
	T4	IIIA	IIIB			IV
H1, P1, CY1, M1						

In the western world institutions, the anatomical localization of lymph node is determined by pathologist on the basis of formalin fixed "en bloc" resected specimen and compliance of these staging systems has been low.

TNM system (UICC/AJCC) has greater prognostic power than the Japanese classification: it is essentially post operative staging.

Japanese classification has been designed as a comprehensive guide to treatment, originally for surgeons and pathologists and today for oncologists and endoscopists as well.

It is chiefly a pre and per operative staging.

New attempts are performed to improve these performances:

- **the ratio metastatic lymph node (RML)** is a ratio between positive and removed nodes: it constitutes for some authors "the most independent prognostic factor in patients with an R_0 resection (41- 46).

- For these authors,the ratio of lymph nodes metastases could be the best criteria for deciding on accurate lymph node dissection and the regimen for adjuvant therapy.

- At least, it should be observed that **Maruyama index** of unresected disease or Maruyama index (MI) allows to estimate the percentage likelihood of nodal involvement for each regional lymph node station(1.12) left in situ per patient's surgeon thanks to a computer program. For the benefit of those unfamiliar with this tool, the Maruyama computer program simply watches a given case with other similar cases previously treated at the national cancer center in Tokyo.

- The large number of cases in the NCC Tokyo database (daily expanded) serves to make the model predictions of this computer program highly

accurate, not only for Japanese cases but those from Germany and Italy as well (47).

- All of these staging systems have a purpose among others to choose those of patients who are fit for adjuvant therapy.

  This is an exciting perspective as showed by Mc Donald Trial (27), but one has to be aware of mass risk of surgical undertreatment, because of the excessive rely upon chemoradiotherapy to cure the gastric cancer: in the Mc Donald's trial, 54% of patients had D_0: it is incredible.

  On the whole, performing a correct gatrectomy with D_2 lymph nodes resection dictates some operative skills and intensive post operative care.

- With a pathologist inclined to perform largely histopathologic examination of all the harvested lymph nodes.

- Attempting the most rigorous staging possible.

- In specialized institutions (High volume hospital).

- This D_2 lymphadenectomy should avoid splenopancreatectomy if neither spleen nor the pancreas is involved or concerned by the tumor.

  For this purpose it has been proposed a technical refinement: the so called over D_1 or $D_{1.5}$ dissection (Furukawa 48).

- We have also to initiate large randomized clinical trials with subgroups stratifications in order to minimize the possibility of stage migration due to larger LN numbers examined by selecting the highest nodal stage category (N_3) (49).

Perspectives:

- Tools as sentinel lymph node biopsy are currently being developed to identify patients with high risk of lymph node metastases which could influence the extent of surgery(50)

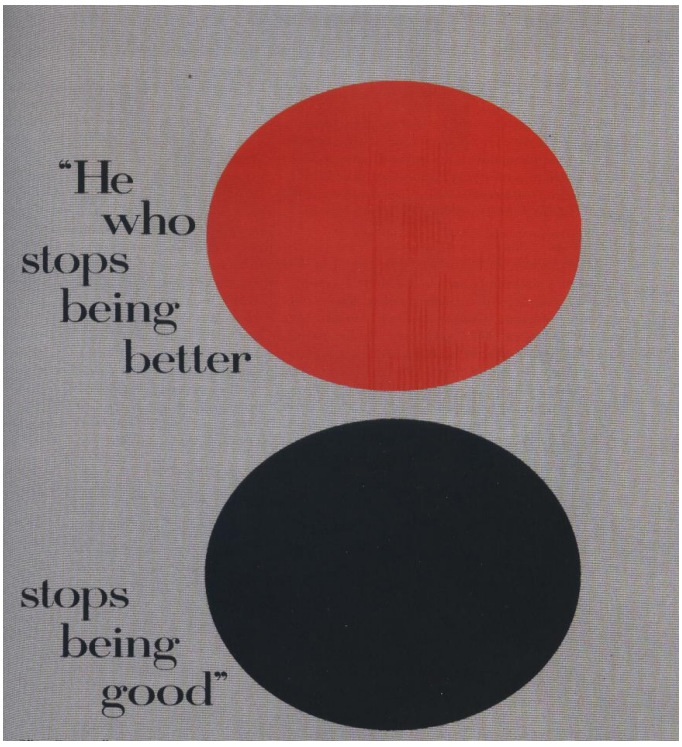
- Genomic profiling of gastric adenocarcinoma using microassay analysis of chromosomal copy number which also seems to be a promising developpement enabling more tailored treatment. (51).

  Conclusions:

  Where are we?

  When we consider the Japanese guidelines (52)

, D_2 gatrectomy is clearly defined as standard surgery for advanced gastric cancer while the British cancer guidance discourages D_2, based on the poor results of the two western RCTs (53).



References

1- SASAKO,M; Maruyama, k; KINOSHITA, T; BONENKAMP, J; Van de Velde, CJH; Hermans, J *« A multicenter prospective, randomized controlled study on the surgical treatment of gastric cancer » JPn J Clin Oncol 1992-2 (1): 41-48*

2- Kajitani,T *Japanese Research society for gastric cancer. "The general rules for the gastric cancer study in surgery and pathology" Part I. Clinical classification. JPN.J.Surg 1981.11: 127-39*

3- NOGUCHI, Y; Imada, T; MATSUMOTO, A; COIT, DG; BRENNAN, M *Radical surgery for gastric cancer : a review of the Japanese experience . Cancer 1989 64: 2053-62*

4- Maruyama, K; Okabayashi, K; Kinoshita, T *Progress in gastric cancer surgery in Japan and its limits of radicality. World.J.Surg 1987: 11: 418-426*

5- Maruyama, K; SASAKO, M; KINOSHITA, T et al *« Should systematic lymph node dissection be recommanded for gastric cancer ? » Eur.J.Cancer 1998- 34: 1480-9*

6- FUCHS, CS; Mayer, RJ *Gastric carcinoma.New Engl.J.med 1995 – 333: 32-41*

7- Roukos, DH *Current status and future perspectives i n gastric cancer management. Cancer Treat Rev 2000. 26: 243-55*

8- Mc Neer, G; Lawrence, W; Ortefa, LG; Sunderland, DA *Early results of extended total gastrectomy for cancer. Cancer 1956- 9: 1153-9*

9- Piso, P; Werner, U; Lang, H et al *Proximal versus distal gastric carcinoma- what are the differences. Annals of Surgical Oncology 2000 – 7 (1): 520-5*

10- Harrison, LE; Karpeh, MS; Brinnam, ME *Total gastrectomy is not necessary for proximal gastric cancer.Surgery 1998; 19: 523-31*

11- Sano, T; KATAI, H; SASAKO, M et al *One thousand consecutive gastrectomies without operative mortality. Br.J.Surg . 2002- 89: 123*

12- Alan GK, li *" An overseas perspective of evolving gastric cancer practices in japan" Japanese Journal of clinical oncology. 2005- 35 (3): 165-167*

13- RAMIREZ, MP *The myth of thin patients as explanation for the excellent results of the Japanese technique in the surgical treatment of gastric cancer. JPN J Clin Oncol 2006- 36 (1) : 64*

14- DHAR, DK; Kubota, H; Tachibana, M et al *Body mass index determines the success of lymph node dissection and predicts the outcome of gastric carcinoma patients.Oncology 2 000: 59(1): 18- 23*

15- TANAKA, T; Nagata, C; OBA, S et al *Prospective cohort study of Body Mass Index in adolescence and death from stomach cancer in Japan Cancer Sci: 2007- 98 (11): 1785-9*

16- Nishi, M; Ichikawa, H; Nakajima, T; Maruyama, K; TAHARA, E *Gastric cancer. Springer-Verlag- Tokyo- Berlin- Heidelberg 1993: 319- 330*

17- Blot WJ; Devesa, SS; Kneller, RW et al *" Rising incidence of adenocarcinoma of the oesophagus and gastric cardia." Jama 1991- 265: 1287- 89*

18- Maruyama, K *Surgical treatment and end results of gastric cancer. Tokyo national cancer center 1985*

19- Fielding, JWL *Gastric cancer: different diseases.Br J Surg 1989: 76: 1227*

20- ADAM, YG; Efron, E *" TRENDS and controversies in the management of carcinoma of the stomach". Surg.Gyn.obs.1989: 169: 371- 385*

21- Schwartz, RE; Zagala- Nevarez, K *" Ethnic survival differences after gastrectomy for gastric cancer are better explained by factors specific for disease location and individual patient comorbidity". Eur.J.Surg.Oncol.2002; 29 (3): 214-19*

22- Sackett, D; Rosenberg WMC; Gray Jam; Haynes RB; Richardson, WS *Evidence based medicine: what it is and what isn't? BMJ.1996: 312- 71*

23- Bonenkamp, JJ; Hermans, J; Sasako, M; Van de Velde, CJH *(Dutch gastric cancer group) Extended lymph node dissection for gastric cancer. New.Eng.J.med 1999: 340: 908- 14*

24- Cushieri, A; Weeden, S; Fielding, J et al *Medical research council " Patients survival after D_1 and D_2 resections for gastric cancer: long term results of the MRC randomized surgical trial. Surgical co-operative group". Br.J.Cancer 1999: 79: 1522- 30*

25- Brennan, MF *Lymph node dissection for gastric cancer.The New. Engl.J.med. 1999: 340: 956-958*

26- JUN.HO.LEE *"Learning curve for total gastresctomy with D_2 lymph node dissection: cumulative sum analysis for qualified surgery".Annals of surgical oncology 2006.13 (9) 1175-1181*

27- Mc Donald, JS; Smalley, SR; Benedetti, J et al *Chemoradiotherapy after surgery alone for adenocarcinome of the stomach on gastro-oesophageal junction.N.Engl.J.med 2001: 345- 30*

28- Warren, WD *Controlled clinical research opportunities and problems for the surgeon (presidential address to the society for surgery of the alimentary tract 1973) Am J Surg 1990 160: 4-8*

29- Roukos, DH; Lorenz, M; Encke, A *Evidence of survival benefit of extended lymphadenectomy in western gastric cancer patients based on a new concept. A prospective long term follow up study. Surgery 1998- 123: 573-8*

30- Siewert, JR; Boettcher, K; Stein, HJ et al *Relevant prognostic factors in gastric cancer. Ten year results of the german gastric cancer study. Ann Surg 1998.228: 449-61*

31- Roviello, F; Marelli, PM; De Manzenni, G *Survival benefit of extended D_2 lymphadenectomy in gastric cancer with involvement of second level lymph nodes: a longitudinal multicenter study. Annals of surgical oncology 2002.9: 894-900*

32- Volpe, CM; Koo, J; Miloro, SM et al *The effect of extended lymphadenectomy on survival in patients with gastric adenocarcinoma. J.am.coll.surg 1995 181: 56- 64*

33- Bozzetti, F; Marubini, E; Bontant, G et al *Subtotal versus total gastrectomy for gastric cancer : a five survival rate in a multicenter randomized Italian trial- Italian gastro-intestinal tumor study group.Ann Surg 1999 230: 170-178*

34- Degiuli, M; Sasako M; Pouti, A et al *Morbidity and mortality after D_2 gastrectomy for gastric cancer results of the Italian gastric study group prospective multicenter surgical study.J.Clin oncol 1998 16 1490- 1493*

35- Sano, J; Sasako, M; Yamamoto, S et al *" Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D_2 and extended paraaortic lymphadenectomy" Japan clinical oncology group study 9501. Journal of clinical oncology 2004 22 (14): 2767- 73*

36- Hartgrink, HH; Van de Velde, CJH; PUTTER, H et al *Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized dutch gastric cancer group trial. Journal of clinical oncology 2004 22 (11): 2069-2077*

37- Feinstein, AR; Sosin, DM; Wells CK *The Will Rogers phenomenon. Satge migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. N.Engl.J.med 1985: 312: 1604-8*

38- Sobin L; Wittekingch.editors *TNM classification of malignant tumors – 6th Ed.New York: Wiley-liss; 2002*

39- Aiko, T; Sasako, M *The new Japanese classification of gastric carcinoma: points to be revised. Gastric cancer 1998 – 1: 25- 30*

40- Sayegh, ME; Sano, T; Dexter, S; Katai, H; Fukagawa, T; Sasako, M *TNM and Japanese staging systems for gastric cancer: how do they coexist? Gastric cancer 2004: 7: 140-148*

41- Sasako, M; Mc Culloch, P; Kinoshita, T *New method to evaluate the therapeutic value of lymph node dissection for gastric cancer. Br.J.Surg 1995: 82: 346-51*

42- Siewert, TA; Böhcher, K; Stein, HJ et al *German gastric carcinoma study group. Relevant prognostic factors in gastric cancer: ten years results of the German gastric cancer study. Ann Surg 1998 – 228: 449- 61*

43- YU, W; Choi, GS; Whang, I *Comparison of five systems for staging lymph node metastasis in gastric cancer.Br J. Surg 1997 84: 1305- 9*

44- NITTI, D; Marchet, A; Olivieri, M et al *Ratio between metastatic and examined lymph nodes is an independant prognostic factor after D2 resection for gastric cancer: analysis of a large European monoinstitutional experience. Annals of surgical oncology 2003- 10: 1077-85*

45- Kodera, Y; Schwartz, 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 (6) : 855-64*

46- Bando, E; Yonemura, Y; Taniguchi, k et al « *Outcome of ratio of lymph node metastasis in gastric carcinoma » Annals of surgical oncology 2002: 9: 775- 84*

47- Kampschoer, G; Maruyama, K; Van de Velde, CJH et al *Computer analysis in making preoperative decisions : a rational approach to lymph node dissection in gastric cancer patients. Br J Surg 1989- 76: 905- 8*

48- Furukawa, H; Hiratsuka, M; Ishikawa, O et al *Total gastrectomy with dissection of lymph nodes along the splenic artery: a pancreas preserving method. Annals of surgical oncology 2000*

49- Schwartz, RE; Smith, D *Clinical impact of lymphadenectomy extent in resectable gastric cancer of advanced age. Annals of surgical oncology 2006 (14/2): 317- 328*

50- Van de Velde, CJH; PEETERS, KCMJ *The gastric cancer treatment controversy.*

Journal of Clinical Oncology 2003- 21 (12): 2234-6

51- Weiss, M " *Genomic profiling of gastric cancer predicts lymph node status and survival". Oncogene 2003 22: 1872- 73*

52- Nakajima, T *Gastric cancer treatment guidelines in Japan. Gastric cancer 2002 5: 1- 5*

53- Allum, WH; Griffin, SM; Watson, A; Colin-Jones, D *On behalf of the Association of Upper gastro-intestinal surgeons of Great Britain and Ireland, the british society of ! gastro-enterology and the br€itish Association of surgical oncology. Guidelines for the management of oesophageal and gastric cancer.Gut*

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