GASTRIC CANCER

RANDOMIZED CONTROLLED TRIAL ON D2 LINPHADENECTOMY VS STANDARD D1 LINPHADENECTOMY

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The disease

Although its recent worldwide decrease, gastric cancer is nowadays the second cause of mortality for cancer in the word.

At present , in Italy the standardized incidence rate is about 15-20 out of 100000 people per year, with differences among regions.

Overall 5 years survival rate is about 65% in Japan, 35% in Germany, 31% in Italy and 26% in USA (1).

In Turin overall 5 years survival rate of all new cases from 1985 to 1987 was 18% and relative survival rate was 23%. (data from Registro Tumori Piemonte).

While in the 60's and the 70's, the worldwide debate was focused on the extension of gastric resection, in the 80's and the 90's this discussion was shifted over the extension of lymph node dissection during surgery, based on impressive results of japanese authors who routinely performed enlarged lymphadenectomy (2).

Lymph node methastases

Gastric lymph-nodes are classified in 16 main regional stations, grouped into 4 levels (N1 – N4); the number (1-16) of the stations contained into each level varies according to the location of the tumor. Overall, N1 stations (stations number 1, 2, 3, 4, 5 and 6) represent perigastric lymph-nodes while N2 stations (stations number 7,8,9,10,11) are localized along left gastric artery, splenic artery, common hepatic artery and celiac artery and N3 stations (12,13,14) are localized along the hepato-duodenal ligament, the posterior face of the pancreas head and the superior mesenteric vessels. N4 stations (stations number 15 and 16B1) represent middle colic and para-aortic lymph-nodes. (3)

About 75% of new cases of gastric cancer present with lymph-node methastases at the moment of the diagnosis; half of them have already at least N2 lymph nodes involved.

Also 20% of early gastric cancer (EGC, I.e. pT1) are classified as pN+ at the moment of diagnosis and 10% of them are classified as pN2 (2)

The role of lymph node dissection

Overall 5 years survival in recent Japanese studies (mainly from National Cancer Center Hospital, NCCH) is 97.6% in N0 Gastric Cancer, 76% in N1, 39,5% in N2 and 5% in N3 patietns. (2)

Maruyama et al. showed that the extent of lymphadenectomy correlates with survival. In eastern country retrospective series, a complete dissection of level 1 and 2 lymph-nodes (D2 lymphadenectomy) was documented to show better survival rates as compared to the simple standard dissection of level1 (D1 lymphadenectomy). Large series from National Cancer Center Hospital (NCCH, Tokyo) showed overall 5 years survival rates of 60,5% after D2- , 31.4% after D1- and 15.1% after D0-lymphadenectomy. In multivariate analysis the extent of lymphadenectomy was tocumented to represent the fourth independent risk factor, behind T stage, lymph-node metastasys and distant metastasys.

The rationale of a systematic enlarged lymph node removal is represented by the expected decrease of local recurrence rate; in fact local recurrence was documented in 38% of patients reported in series from 60's and 70' and only in 16% of patients from series of 80's and early 90's, when the extended procedure was already routinely applied in far East.

These data from Japanese series (4) have not been confirmed in western countries studies: Gilbersten (USA) reported a decrease of the overall survival from 12.2% to 8.8% after the extended procedure. And also the two main european trials, the MRC (5) and the Dutch (6) randomized controlled trials do not show any significant improve of survival after D2 lymphadenectomy as compared to the standard D1 procedure, while documenting an impressive increase of postoperative morbidity and mortality.

Feasability of lymphadenectomy

In Japanese observational studies D2 lymphadenectomy is almost always feasible and is not followed by any increase of operative mortality (0.5% in Maruyama series (7)) and post operative complications. On the opposite, western retrospective studies have reported high postoperative mortality and morbidity rates after the extended procedure and also the two recent prospective RCTs have documented an impressive increase of operative mortality (13 vs 6.5%, Cuschieri and 10 vs 4%, Bonenkamp) and morbidity (43 vs 25% Bonenkamp e 46 vs 28% Cuschieri) when the extended lymphadenectomy is compared to the standard limited D1 lymphadenectomy. (5,6)

Our (IGCSG) previous one arm phase II prospective trial on D2 lymph node dissection with pancres preserving technique and quality control has documented successful data on operative mortality (3%) and morbidity (21%); the figures published are even lower than those reported in previous rectrospective western series after D1 lymphadenectomy and very close to Japanese results.

Study Design

After diagnosis, definition of pre-operative inclusion criteria and informed consent have been obtained, patients will undergo exploratory laparotomy for hystopathological extemporaneous examination of peritoneal lavage (*sediment citology*) and 16B1 lymph node station and complete definition of inclusion criteria (H0, P0, T<4, N2-N3-N4 neg, absence of neoplastic cells on peritoneal lavage). Eligible patients will be randomized to receive standard D1- or extended D2- lymphadenectomy.

Patients will not receive adjuvant radio-chemotherapy

Patients will be followed up every 4 months for the first 2 years and then every 6 months for at least 5 years.

Data concerning descriptions and details on diagnosis, surgery, complication and hystopathological examination will be recorded at each institution by a local data collector and sent to Dr. A Vendrame (Data Manager) c/o Dipartimento Oncologico, II Div. Chirurgica, Osp S. Giovanni Antica Sede – Torino – Fax n. 0115175555 (alvendra@libero.it) , within 30 days of patients' discharge or death. Records concerning Follow-up details will be sent at least every 6 months.

Endpoints

primary endpoint:

overall survival (defined as the time from randomization to death) of D1 and D2 arms;

secondary endpoints:

- disease specific survival defined as the time from randomization to death from gastric cancer progression
- recurrence-free survival defined as the time from randomization to the first documentation of cancer recurrence or death from any cause
- procedure related morbidity and mortality (intraoperative mortality or mortality within 30 days from operation)

Patients' selection

Inclusion criteria

histological demonstration of gastric carcinoma

age <= 80 years old

Elective surgery

Informed consent

At the time of laparotomy:

- Absence of liver or peritoneal metastases
- Absence of neoplastic macroscopic involvement of adjacent structures (< T4) (the need of surgical removal of the involved organ represents a criterium for exclusion
- Lymph-node stage N0-N1
- absence of cancer cells in peritoneal washing fluid at intraoperative extemporaneus examination (*sediment citology*)
- Radical surgery, absence of microscopic and macroscopic residual tumor (R0);
- no involvement of the hoesophagus, GE junction and duodenum

Exclusion criteria

Severe improvement of cardiac, metabolic or renal function (ASA >=4)

Need for Emergency surgery

metastases in lymph-node station 16B1 (LN around the abdominal aorta from the lower margin of the left renal vein to the upper margin of the inferior mesenteric artery) at intraoperative extemporaneous pathological examination

macroscopic massive and diffuse involvement of N2 stations (bulky enlargement of nodes around the celiac axis)

distant metastases

previous gastric surgery

previous or co-existing cancer outside stomach

Surgery

Gastrectomy

Each procedure (total/subtotal gastrectomy, D1/D2 lymphadenectomy) starts with a complete inspection of the abdominal cavity in order to define H and P factors (absence of liver and peritoneal metastases); afterwords a peritoneal washing with 250 cc of Saline Solution is performed to exclude the presence of cancer cells through extemporaneous *sediment cytology*. Than mobilization of the duodenum and pancreatic head (*Kocher maneuvre*) will allow to collect a 16B1 station Lymph-nodes sample (N3) for hystopathological extemporaneous examination.

If extemporaneous sediment cytology and hystopathology on lymph-node sample are negative and N2 stations lymph-nodes are macroscopically not diffusely involved, the patient will be considered as eligible and randomized.

A distal gastrectomy (DG) is performed when the proximal edge of the tumor is more than 3 cm from the cardia in EGC and in Bormann type 1 and 2 AGC. On the opposite, a TG is required every time these conditions are not met and, in addition, when the tumor is located close to the greater curvature, beyond Demel's point, and in case of *linitis plastica.*[15]

Splenectomy

Upper third tumors

Splenectomy, as described in Maruyama ''pancreas preserving technique'', is recommended in upper third T2/T3 tumors located on the grater curvature or on the anterior/posterior surface next to the grater

curvature. Splenectomy is not recommended when tumors are located on the lesser curvature or on the anterior/posterior surface next to the lesser curvature; it is not indicated in case of EGC, irrespective of tumor location.

Middle third tumors

Splenectomy is recommended when T2/T3 tumors are located on the grater curvature or on the anterior/posterior surface next to the grater curvature, supplied by left gastro-epiploic vessels and drained by splenic-hilum station (nr 10) lymph-nodes. Splenectomy is not recommended when blood supply comes from right gastro-epiploc vessels, when tumor is located on the lesser curvature or on the anterior/posterior surface next to the lesser curvature and in case of EGC irrespective of tumor location.

Lower third tumors

Splenectomy is not recommended

There are no specific indications to reconstruction techniques after distal and total gastrectomy.

5.2 D1 lymphadenectomy

D1 Lymphadenectomy Is defined as the removal of level 1 (N1) lymph node stations depending on tumor site, as follows:

Upper third tumors

lymph node station nr 1 (right para-cardial)

lymph node station nr 2 (left para-cardial)

lymph node station nr 3 (along the lesser curvature)

lymph node station nr 4sa (grater curvature along the short gastric vessels)

lymph node station nr 4sb (grater curvature along the left gastroepiploic vessels)

Middle third tumors

lymph node station nr 1 (right para-cardial)

lymph node station nr 3 (along the lesser curvature)

lymph node station nr 4sa (grater curvature along the short gastric vessels)

lymph node station nr 4sb (grater curvature along the left gastroepiploic vessels)

lymph node station nr 5 (suprapyloric)

lymph node station nr 6 (infrapyloric)

Lower third tumors

lymph node station nr 3 (along the lesser curvature)

lymph node station nr 4sa (grater curvature along the short gastric vessels)

lymph node station nr 4sb (grater curvature along the left gastroepiploic vessels)

lymph node station nr 4d grater curvature along the right gastroepiploic vessels)

lymph node station nr 5 (suprapyloric)

lymph node station nr 6 (infrapyloric)

Diffuse gastric cancer

lymph node station nr 1 (right paracardial)

lymph node station nr 2 (left paracardial)

lymph node station nr 3 (along the lesser curvature)

lymph node station nr 4sa (grater curvature along the short gastric vessels)

lymph node station nr 4sb (grater curvature along the left gastroepiploic vessels)

lymph node station nr 4d (grater curvature along the right gastroepiploic vessels)

lymph node station nr 5 (suprapyloric)

lymph node station nr 6 (infrapyloric)

A complete removal of station nr 4sa lymph-nodes should entail splenectomy

5.3 D2 linphadenectomy

D2 lymphadenectomy entails the removal of level 1 and 2 (N1 and N2) lymph-node stations , depending on tumor location, as follows:

Upper third tumors

lymph node station nr 1 (right para-cardial)

lymph node station nr 2 (left para-cardial)

lymph node station nr 3 (along the lesser curvature)

lymph node station nr 4sa (grater curvature along the short gastric vessels)

lymph node station nr 4sb (grater curvature along the left gastroepiploic vessels)

lymph node station nr 4d (grater curvature along the right gastroepiploic vessels)

lymph node station nr 7 (along the left gastric artery)

lymph node station nr 8a (anterior the common hepatic artery, anterosuperior group)

lymph node station nr 9 (around the celiac artery)

lymph node station nr 10 (at the splenic hilum) (only if splenectomy is performed)

lymph node station nr 11p (along the splenic artery, proximal to the emergency of the posterior gastric artery)

lymph node station nr 11d (along the splenic artery, distal to the emergency of the posterior gastric artery)

lymph node station nr 5 (suprapyloric)

lymph node station nr 6 (infrapyloric)

Middle third tumors

lymph node station nr 1 (right para-cardial)

lymph node station nr 3 (along the lesser curvature)

lymph node station nr 4sa (grater curvature along the short gastric vessels)

lymph node station nr 4sb (grater curvature along lthe eft gastroepiploic vessels)

lymph node station nr 5 (suprapyloric)

lymph node station nr 6 (infrapyloric)

lymph node station nr 7 (along the left gastric artery)

lymph node station nr 8a (along the common hepatic artery, anterosuperior group)

lymph node station nr 9 (around the celiac artery)

lymph node station nr10 (at the splenic hilum) (only if splenectomy is performed)

lymph node station nr 11p (along the splenic artery, proximal to the emergency of the posterior gastric artery)

lymph node station nr 11d (along the splenic artery, distal to the emergency of the posterior gastric artery)

Lower third tumors

lymph node station nr 3 (along the lesser curvature)

lymph node station nr 4sa (grater curvature along the short gastric vessels)

lymph node station nr 4sb (grater curvature along the left gastroepiploic vessels)

lymph node station nr 4d (grater curvature along the right gastroepiploic vessels)

lymph node station nr 5 (suprapyloric)

lymph node station nr 6 (infrapyloric)

lymph node station nr 7 (along the left gastric artery)

lymph node station nr 8a (along the common hepatic artery, anterosuperior group)

lymph node station nr 9 (around the celiac artery)

lymph node station nr 1 (right paracardial)

lymph node station nr 10 (at the splenic hilum) (only if splenectomy is performed)

lymph node station nr 11p (along the splenic artery, proximal to the emergency of the posterior gastric artery)

lymph node station nr 12a (in the hepatoduodenal ligament, along the hepatic artery)

lymph node station nr 14v (along the superior mesenteric vein)

Diffuse tumor

lymplymph node station nr 1 (right paracardial)

lymph node station nr 2 (left paracardial)

lymph node station nr 3 (along the lesser curvature)

lymph node station nr 4sa (grater curvature along the short gastric vessels)

lymph node station nr 4sb (grater curvature along the eft gastroepiploic vessels)

lymph node station nr 4d (grater curvature along the right gastroepiploic vessels)

lymph node station nr 5 (suprapyloric)

lymph node station nr 6 (infrapyloric)

lymph node station nr 7 (along the left gastric artery)

lymph node station nr 8a (along the common hepatic artery, anterosuperior group)

lymph node station nr 9 (around the celiac artery)

lymph node station nr 10 (at the splenic hilum) (only if splenectomy is performed)

lymph node station nr 11p (along the splenic artery, proximal to the emergency of the posterior gastric artery)

lymph node stations nr 11d (along the splenic artery, distal to the emergency of the posterior gastric artery)

lymph node station nr 12a (in the hepatoduodenal ligament, along the hepatic artery)

lymph node station nr 14v (along the superior mesenteric vein)

At least 25 lymph-nodes have to be harvested.

9. Postoperative evaluation

Data on post-operative course (hospital stay, need for blood transfusion, post-op bowel flatus and movement, abdominal lymphatic drainage), early (within 30 days) or late complications will be collected and reported on patient's page.

Hospital mortality will be evaluated (within 30 days)

10. Follow-up

Follow-up is scheduled every 4 months during the first two years and every 6 months for at least 3 years. Follow up examinations : nutritional biomarkers, tumor markers , abdominal US and chest X-ray each time; abdominal CT scan each year or on demand; endoscopy each year or on demand; others on demand.

11. Statistics

This is a multicenter, parallel, individually randomised superiority trial with balanced randomisation (allocation ratio 1:1) conducted in Piedmont, Italy.

Sample size

The size of the study is calculated on the primary outcome, which is overall survival rate. To detect with a statistical power of 80% an absolute increase in 5-year survival of 15% in patients allocated to D2 (from 30% after D1 to 45% in the D2 group) the sample size is set at 160 patients per arm. Survival estimates is set according to the literature and, for the D2 group, based on a previous phase II study on a cohort of D2 patients (De Giuli, 1998).

Randomisation and blinding

Treatment allocation is performed by the project statisticians using random permuted blocks with fixed number (n=10) per block, stratified by surgical unit. The allocation ratio is 1:1. The sequence is generated by use of a random-number table. The randomisation procedure and the size of the blocks are concealed to the surgeons. The Department of Oncology, Division of Surgery, San Giovanni A.S. Hospital, Turin is the centralised randomisation centre. Patients who fullfills the eligibility criteria during laparotomy are registered by phone call to the randomisation centre. In order to assure its concealment, allocation to the experimental arm (D2) or usual care (D1) is contained in sequentially numbered, opaque, sealed envelopes which the randomisation centre receives from the statistical Unit. The operator at the randomisation centre completes the patient-form data indicating the surgical unit, time and date of randomisation and randomisation number, then openes the envelope and immediately communicates patient allocation to the surgical unit. Each surgical unit maintaines a sequential register with information on each randomised patient. All patients with a gastric cancer undergoing surgery in each surgical unit (eligible or non-eligible) aro also registered. Due to the nature of the intervention, nor patients or care providers can be blinded to treatment allocation. Outcome is assessed blind of treatment allocation by follow up for mortality and cause of death performed by the Piedmont Cancer Registry.

Statistical analysis

A safety interim analysis is foreseen in the study protocol for assessment of post-operative morbidity and complications only. It will be performed on the first 160 patients recruited (50%). No interim analysis will be performed on the primary outcome. The Kaplan-Meier method will be used to estimate survival curves for overall and disease free survival. The log-rank test will be used to evaluate the survival curves. Potential prognostic factors (age, pT, pN and type of resection) will be entered into a Cox's regression model. All analyses will be undertaken on an intention-to-treat basis, regardless of the treatment actually received. Continuous and categorical outcome variables wil be analysed by Student's *t* test (or the Mann–Whitney test) or by $\chi 2$ test (or Fisher's exact test), respectively. Statistical significance is set at the 0.050 level. The R environment (http://www.rproject.org) is used for all statistical analyses.