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**Towards curative therapy in gastric cancer: faraway, so close!**

Cravo M *et al*. Gastric cancer: faraway, so close!

Marília Cravo, Catarina Fidalgo, Rita Garrido, Tânia Rodrigues, Gonçalo Luz, Carolina Palmela, Marta Santos, Fábio Lopes, Rui Maio

**Marília Cravo, Catarina Fidalgo, Rita Garrido, Tânia Rodrigues, Gonçalo Luz, Carolina Palmela, Marta Santos, Fábio Lopes, Rui Maio,** Gastroenterology, Surgery and Oncology Clinics, Hospital Beatriz Ângelo, 2674-514 Loures, Portugal

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**Correspondence to: Marília Cravo, MD, PhD,** Gastroenterology Department, Hospital Beatriz Ângelo, 2674-514 Loures, Portugal. marilia.cravo@hbeatrizangelo.pt

**Telephone:** +351-919-439192

**Fax:** +351-219-847209

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**Abstract**

Although recent diagnostic and therapeutic advances have improved substantially the survival of patients with gastric cancer (GC), the overall prognosis is still poor. Surgery is the only curative treatment and should be performed in experienced centers. Due to high relapse following surgery, complementary and systemic treatment aimed at eradicating micrometastasis should be performed in most cases. Cytotoxic treatments are effective in downstaging locally advanced cancer but different sensitivities and toxicities probably exist in different GC subtypes. Current treatment protocols are based primarily on clinical data and histological features but molecular biomarkers which would allow prediction of treatment responses are urgently needed. Host factors responsible for inter-individual variability of drug response or toxicity will also contribute to develop more effective and less toxic treatments.

**Key words:** Gastric cancer; Multidisciplinary treatment; Therapeutic strategies; Curative surgery

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**Core tip:** A lot of progresses have been accomplished in the past decades in regard to identifying risk factors for gastric cancer as well as to unravel its pathogenesis. Diagnostic and therapeutic management of this disease has improved a lot in the past decade. Despite this, prognosis remains dismal and new therapeutic options are urgently needed. Hopefully, in the years to come, treatments will probably be individualized both to tumor characteristics and host factors with the aim of increasing the efficacy of therapy as well as decrease its toxicity. Faraway, so close!

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**INTRODUCTION**

Gastric cancer (GC) is a major public health issue as the fourth most common cancer and the second leading cause of cancer-related death[[1](#_ENREF_1)]. It is usually diagnosed at an advanced stage and, consequently, the prognosis remains dismal. Although surgery is the definitive therapy, rates of recurrence are high, creating the need for neoadjuvant or adjuvant therapy. These have improved significantly the 5-year survival of these patients but not all patients benefit equally from these treatment options. The ability to predict whether patients will respond to specific therapies would be of particular value and would allow for stratifying patients for personalized treatment strategies, probably with less toxicity. Recent advances have improved our understanding of gastric carcinogenesis with an unprecedented opportunity of developing novel therapeutic strategies. Exploring and validating tissue-based biomarkers are ongoing processes, which will certainly open new avenues for treating and improving the prognosis of patients with GC.

**RISK FACTORS FOR GC**

Like other human cancers, GC is the end result of the interplay of environmental and susceptibility factors. The striking geographic variation in GC incidence should reflect early environmental exposure rather than genetics, as migration studies have confirmed a decline in incidence in subsequent generations. The only environmental factor that is considered to be a type I carcinogen by the World Health Organization is *Helicobacter pylori* (*H. pylori*)[[2](#_ENREF_2)]. This bacterium can have a lifelong uneventful relation with its host but, in a minority of cases, causes peptic ulcer, both intestinal and diffuse type gastric adenocarcinoma or gastric MALT lymphoma. About 50% of the world’s population is infected by *H. pylori*, but fewer than 0.5% of infected individuals will develop GC. This disparity reflects variation in the pathogenicity of bacterial strains as well as host inflammatory genetic susceptibility factors such as IL-1B, IL-8, IL-10, IFN-gamma and TNF-B polymorphisms[[2](#_ENREF_2)]. *H. pylori* infection causes chronic inflammation, accumulation of reactive oxygen species (ROS) and oxidative damage in the gastric mucosa, thereby promoting the sequential progression of normal gastric epithelium through atrophic gastritis, intestinal metaplasia, and dysplasia to carcinoma. Advanced atrophic corpus-predominant gastritis and subsequent development of intestinal metaplasia provides the histological base for GC genesis[[3](#_ENREF_3)]. This model of precancerous lesions is currently accepted and surveillance recommendations apply to patients at increased risk[[3](#_ENREF_3)]. The intestinal-type GCs are more related to atrophic gastritis, intestinal metaplasia and dysplasia, but *H. pylori* infection is also associated with an increased risk of diffuse-type GC.

In addition to *H. pylori*, dietary and lifestyle factors may also modify the risk of developing GC. Low socioeconomic status and associated conditions, have been associated with a two-fold increase in GC risk[[4](#_ENREF_4)]. Subjects belonging to a low socioeconomic status have a higher prevalence of *H. pylori* infection, more frequent smoking habit, and less vegetables and fruit intake, than the general population[[5](#_ENREF_5)]. In an analysis of the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST) there was a 45% higher risk of GC associated with ever smoking compared to never smokers[[6](#_ENREF_6)]. In a meta-analysis with forty-two articles, Ladeiras-Lopes *et al*[[7](#_ENREF_7)] concluded that smoking is the most important behavioral risk factor for GC. Heavy alcohol intake is associated to some excess GC risk, mainly in men[[8](#_ENREF_8)]. Nonetheless, as heavy drinkers usually smoke and have a poor diet, there may be some confounding factors in these conclusions[[4](#_ENREF_4)]. Among dietary factors, N-nitroso compounds (including nitrosamine) are proven animal carcinogens. Potential sources of N-nitroso compounds are beer, processed (smoked, cured, salted, and pre- served) meats, red meat and tobacco smoke[[8](#_ENREF_8)]. In the EPIC cohort, the authors found no association between nitrites and nitrosodimethylamine intake and GC risk, but endogenous production of N-nitroso compounds was significantly associated with noncardia cancer risk[[9](#_ENREF_9)].

A meta-analysis in 2012, including 2076498 patients, showed a significant positive association between high salt intake and GC[[10](#_ENREF_10)]. High salt intake damages gastric mucosa and increases the susceptibility to carcinogenesis in studies with rodents.

In respect to protective factors, intake of non-starchy vegetables and fruits has been associated with a moderately decreased risk of GC in many cohort, population- and hospital-based case-control studies[[4](#_ENREF_4),[5](#_ENREF_5)]. In a reanalysis of the EPIC cohort, a negative and significant association was observed between the total vegetable, fruit, flavonoid intake and dietary total antioxidant capacity and risk of GC[[11-13](#_ENREF_11)]. This protection afforded by vegetables and fruits may derive from their content in antioxidants (such as vitamin C), which may reduce with the formation of N-nitroso compounds in the stomach[[5](#_ENREF_5)].

A recent large European prospective cohort study investigated the combined impact of the above-cited behaviors on GC risk, using a healthy lifestyle index[[14](#_ENREF_14)]. The authors concluded that adopting a combination of lifestyle behaviors, including not smoking, limiting alcohol consumption, following a healthy dietary pattern (represented by the Mediterranean diet) and having a normal body mass index can dramatically decrease the burden of GC. In 2003, in a meta-analysis by Wang *et al*[[15](#_ENREF_15)] including 2831 GC patients, regular NSAIDs users had a reduced risk of GC (OR = 0.78, 95%CI: 0.69–0.87). These results have recently been confirmed in a wide systematic review[[16](#_ENREF_16)]. Probably the pro-apoptotic and anti-angiogenesis effects of NSAIDs known to inhibit carcinogenesis in patients with colonic polyps act in a similar way in gastric mucosa[[4](#_ENREF_4)]. No randomized controlled studies exist to date on the long-term effect of NSAID alone on the development of GC and the alleged protective effect could simply reflect the «protective user effect» as most individuals eligible for sustained NSAID chemoprophylaxis do not usually suffer from gastric disease.

The decrease of distal GC prevalence that has been consistently described in a number of studies[[17](#_ENREF_17)], could very well be the result of life style changes associated with improvement of economic status, better hygiene and consequent decrease of *H. pylori* infection[[4](#_ENREF_4), [5](#_ENREF_5)].

**PATHOGENETIC MECHANISMS OF GASTRIC CARCINOGENESIS**

About 95% of gastric tumors are adenocarcinomas, which can be classified into well differentiated (intestinal), undifferentiated (diffuse), and mixed types. Further knowledge about GC heterogeneity has been enlightened by The Cancer Genome Atlas Research Network. Through the molecular characterization of 295 gastric adenocarcinomas, 4 GC subtypes have been proposed: microssatellite unstable tumors; genomically stable tumors; tumors displaying chromosomal instability and Epstein-Barr positive tumors[[18](#_ENREF_18)]. Hopefully this subtype analysis will allow a tailored therapeutic strategy for selected patients.

Like other cancers, GC is a complex, multistep and molecularly heterogeneous disease, involving deregulation of canonical oncogenic pathways such as p53, Wnt/B-catenin, and nuclear factor (NF)-kB, among others. While most intestinal-type of GCs progress through the multistep cellular dedifferentiation described by Correa *et al*[[19](#_ENREF_19)], most of the diffuse-type of cancers involve the sporadic or syndromic loss of expression of adhesion protein E-cadherin (CDH1). This is a calcium dependent cell-to-cell adhesion glycoprotein which plays a critical role in maintaining the normal epithelium architecture. The cytoplasmic domain of this molecule interacts with B-catenin, forming strong cohesive nets between the actin cytoskeleton, essential for processes of cell-cell adhesion. Inactivation of CDH1 by mutation, deletion or aberrant methylation leads to enhanced cellular motility resulting in tumor dedifferentiation and invasiveness[[20](#_ENREF_20)]. Inactivation of CDH1 has been described in over 50% of diffuse GC but also in a small proportion of intestinal-type tumors[[20](#_ENREF_20)].

***Stem cell hypothesis***

Most of the molecular events described above have been extensively characterized. Irrespective of the type or order in which these events occur thereby promoting gastric carcinogenesis, the stem cell hypothesis states that tumors are heterogeneous and there is a subset of cells capable of self-renewal, asymmetrical division and differentiation with the ability of generating a new tumor. Takaishi *et al*[[21](#_ENREF_21)] identified CD44 as a gastric stem cell marker. The origin of cancer stem cells (CSCs) could be differentiation of epithelial stem cells (epithelial–mesenchymal transition) or recruitment of bone marrow derived stem cells (BMDSCs). Houghton *et al*[[22](#_ENREF_22)] published a breakthrough paper on Science in 2004 claiming that GC could originate in the bone marrow. Using a model of helicobacter infected mice, the authors proved there was recruitment of bone marrow derived stem cells (BMDSCs) that repopulated the gastric epithelium and progressed from metaplasia to dysplasia and later to intra-epithelial cancer. The proposed explanation is that chronic inflammation induced by *H. pylori* promotes cytokine release and mesenchymal stem cell recruitment from the bone marrow. These bone marrow stem cells are capable of homing to the stomach epithelium and differentiate into gastric cells through fusion[[23](#_ENREF_23)].

One of the most important steps in carcinogenesis is the moment when cancer becomes a systemic disease. The epithelial-to-mesenchymal transition (EMT) is the developmental process through which epithelial cells acquire the migratory capacities of mesenchymal cells. These mechanisms involve replacement of E-cadherin by N-cadherin, metalloproteinase increase and transcription of Snail and ZEB[[24](#_ENREF_24)]. Very recently, Choi *et al*[[25](#_ENREF_25)] proved that *H. pylori* induces epithelial-mesenchymal transition by comparing the expression of TGF-B1 and EMT markers (Twist, Snail, Slug, vimentin and E-cadherin) in controls, patients with gastric dysplasia and early GC (EGC) before and after *H. pylori* eradication with a follow up of 46 months. TGF-B1, Twist, Snail, Slug, vimentin and CD44 were up-regulated in patients with dysplasia and EGC while E-cadherin was decreased. After *H. pylori* eradication, E-cadherin expression was enhanced while the other markers were reduced. These authors propose that *H. pylori* triggers both EMT pathway and the emergence of gastric stem cells.

As appealing and out of the box as the stem cell hypothesis may be, it has not yet produced specific therapeutic targets and its mechanisms seem too ubiquitous to be targeted.

Although in the past decades remarkable progresses have been made in understanding and identifying genetic and epigenetic events which can drive normal gastric mucosa to cancer, we now need to use proteomic and metabolic approaches to design targeted and effective therapies in patients with GC. Given the role of these molecular events in directing the pathogenesis of GC, studying their signatures and developing them as biomarkers for targeted therapies, is likely to yield significant impact in the outcome of these patients

**THERAPEUTIC STRATEGIES IN GC**

***Perioperative therapies - chemo and chemoradiotherapy***

Currently, surgical resection is the only curative therapy for non-metastatic gastric adenocarcinoma. However, having shown that GC may be a systemic disease from the beginning, it is easily understandable that patients submitted to surgery alone were prone to loco regional or distant recurrences of their disease.

Due to large scale randomized trials demonstrating that preoperative and perioperative chemotherapy (CT) improves the clinical outcome for patients with GC[[26-28](#_ENREF_26)], a standard medical treatment of GC has been defined[[29](#_ENREF_29)]. Patients with potentially resectable tumors are treated with surgery and perioperative CT or postoperative chemoradiotherapy (CRT)[[30](#_ENREF_30),[31](#_ENREF_31)]. In most European countries combined preoperative and postoperative administration of CT as in the multinational MAGIC trial[[27](#_ENREF_27)] is the preferred treatment strategy. In Northern America most Centers perform postoperative CRT according to the large American Intergroup trial (INT0116). The latter is criticized by some as inadequate surgical lymphadenectomy may have led to an overestimation of benefit[[31](#_ENREF_31)]. This is supported by retrospective data from the Dutch D1D2 trial, demonstrating that chemoradiotherapy reduces local recurrence rates following D1 resection but provides no benefit in patients who have undergone D2 resection[[32](#_ENREF_32)].

Cytotoxic therapy provides positive response rates ranging from 20%-60%[[33](#_ENREF_33)] which is a major breakthrough if we think that two decades ago CT was used solely in the palliative setting because GC was considered very little chemosensitive.

Although there are a few studies evaluating clinical and pathological predictors of response and prognostic factors in the neoadjuvant setting, none of the potential markers have been validated in prospective studies[[34-36](#_ENREF_34)].

***Neoadjuvant/ perioperative chemotherapy***

Neoadjuvant chemotherapy is administered as a means of “downstaging” a locally advanced tumor prior to an attempt at curative resection. This approach has been applied to patients thought to have resectable disease as well as those with apparently unresectable but nonmetastatic disease. One proposed advantage is the usually the better compliance to chemotherapy in the neoadjuvant setting. Another benefit of neoadjuvant CT is in patients who are at high risk of developing distant metastases (*e.g.*, those with bulky T3/T4 tumors, visible perigastric nodes) who may be spared the morbidity of unnecessary gastrectomy if evidence of distant metastases emerges after CT.

Three large, adequately powered trials have directly compared surgery with or without neoadjuvant or perioperative CT, two of which demonstrate a survival benefit for this approach[[26-28](#_ENREF_26)]. A meta-analysis of these three trials plus two other trials comparing preoperative oral fluoropyrimidine *vs* surgery alone[[37](#_ENREF_37),[38](#_ENREF_38)] and seven other smaller trials comparing a variety of preoperative CT regimens *vs* surgery alone, concluded that neoadjuvant CT was associated with a statistically significant benefit in terms of both overall survival (OR = 1.32, 95%CI: 1.07-1.64) and PFS (OR = 1.85, 95%CI: 1.39-2.46)[[30](#_ENREF_30)]. Furthermore, neoadjuvant CT was associated with a significantly higher complete (R0) tumor resection rate (OR = 1.38, 95%CI: 1.08-1.78), and did not significantly worsen rates of operative complications, perioperative mortality, or grade 3 or 4 adverse effects (Table 1).

In terms of patient selection for this approach, it is reasonable to utilize the eligibility criteria for the MAGIC trial: patients of any age with a performance status of 0 or 1, a histologically proven adenocarcinoma of the stomach that was considered to invade the muscular propria (T2) and/or with positive lymph nodes N+, with no evidence of distant metastases or locally advanced inoperable disease, as evaluated by Computerized Tomography, ultrasonography, and laparoscopy[[27](#_ENREF_27)].

***Neoadjuvant chemotherapy vs neoadjuvant chemoradiotherapy***

Preoperative combined chemoradiotherapy and radiation therapy (RT) is more commonly used for esophageal, esophagogastric junction (EGJ), and gastric cardia cancers than for potentially resectable non-cardia gastric adenocarcinomas. Neoadjuvant CRT was compared with induction chemotherapy alone in the multicenter German POET[[39](#_ENREF_39)]. Although there were potentially clinically meaningful survival differences that favored CRT, they were not statistically significant. Furthermore, whether the results can be extrapolated to patients with true non-cardia GC is uncertain. The ongoing TOPGEAR trial address the question, whether neoadjuvant CRT is superior to CT in a phase II/III setting[[40](#_ENREF_40)].

***What about adjuvant chemoradiotherapy vs adjuvant chemotherapy?***

Adjuvant CT has been directly compared with adjuvant CRT in several trials[[41-46](#_ENREF_41)], only one of which has shown a significant overall survival benefit for the addition of radiation therapy (RT) to CT[[41](#_ENREF_41)]. In the largest trial, the ARTIST trial, compared with CT alone, the addition of RT to Cisplatin and capecitabine (XP), CRT did not significantly reduce recurrence rates, although in a post-hoc subgroup analysis, patients with nodal metastases had superior disease-free survival with combined therapy as compared with CT alone[[41](#_ENREF_41)]. In the latest update, at a median follow-up of 84 months, three-year disease-free survival (the primary endpoint) was not significantly better in patients who received combined modality therapy[[42](#_ENREF_42)]. The hypothesis that adjuvant CRT may represent a better approach than adjuvant CT for patients with node-positive disease will be tested in a successor trial, the ARTIST- II trial.

The only trial to show a significant survival benefit for the addition of RT, randomly assigned 68 patients undergoing complete resection with a D1 or D2 lymph node dissection. The three-year disease-free survival rate was significantly higher in the CT group (56% *vs* 29%), as was overall survival (68% *vs* 44%)[[45](#_ENREF_45)].

Although studies are still ongoing, the available data does favor the addition of adjuvant radiotherapy in the treatment of GC (Table 2).

The optimal regimen is not established. Acceptable alternatives include epirubicin, cisplatin, and infusional 5-fluorouracil (ECF), as was used in the perioperative MAGIC trial[[27](#_ENREF_27)]. When adjuvant therapy is used, the optimal regimen is not established. Results with adjuvant capecitabine plus oxaliplatin (CAPOX, XELOX), as was used in the CLASSIC trial[[47](#_ENREF_47)]; or XP, as was used in the ARTIST trial[[41](#_ENREF_41)], are not as mature as those of perioperative ECF (as was used in the MAGIC trial) or S-1[[48](#_ENREF_48)].

The optimal time between surgery and postoperative treatment varies widely. In MAGIC trial[[27](#_ENREF_27)] it was to be initiated 6 to 12 wk after surgery, in Intergroup trial (INT0116)[[31](#_ENREF_31)] between 4 to 7 wk and in ACTS-GC[[48](#_ENREF_48)] patients would start within 6 wk after surgery.

Regarding compliance to treatment, MAGIC[[27](#_ENREF_27)] and FCCNLC[[49](#_ENREF_49)] trials reported that postoperative treatment was concluded in only 42% to 50% percent of the patients demonstrating the importance of preoperative chemotherapy and questioning the use of postoperative treatment in perioperative setting.

In conclusion, the optimal way to integrate combined modality therapy has not been definitively established. Decisions are often made based on institutional and/or patient preference. As science moves increasingly toward molecular targeted therapy, biologic agents hold great promise in the treatment of this disease as well.

**CURATIVE SURGERY IN GC**

***Optimal type of gastrectomy and the length of proximal resection margin***

It is of paramount importance to discuss surgical treatment of GC given its central role in the overall management of the disease.

Total gastrectomy (TG) is the recommended therapy for more proximal tumors in order to guarantee an appropriate proximal resection margin (PRM). For distally located, subtotal gastrectomy (SG) was recommended with a PRM of more than 2-3 cm for early GC and 5-6 cm for advanced GC. In patients with poorly differentiated diffuse cancer, infiltration of the proximal resection margin by microscopic tumor deposits was a major concern and TG was classically recommended. However, a randomized controlled trial (RCT)[[50](#_ENREF_50),[51](#_ENREF_51)] assessed the incidence of microscopic resection margin involvement in patients with diffuse type GC, with no statistical significant difference between total and SG and with a similar survival. Furthermore, the authors claim that SG is associated with a better nutritional status and quality of life as compared to TG. There is no total agreement in respect to what should be considered an appropriate PRM in SG. As shown on Table 3 distances recommended by the German Society differ from those proposed by the JGCA.

Nonetheless, if one considers SG in patients with distally located diffuse-type GC, a wider excision with intraoperative frozen section (IFS) of the resection margin is recommended[[52](#_ENREF_52)] because they are more likely to have a positive margin. On multivariate analysis, higher T stage, higher N stage, larger tumor size and diffuse histologic type were significant independent predictive factors for a positive margin[[52-54](#_ENREF_52)]. Studies have shown that, if PRM is confirmed to be negative for malignancy but shorter than the recommended length, further resection for a larger PRM is unnecessary, since the length of PRM has no prognostic impact as long as resection margin is free of tumor[[55](#_ENREF_55)].

When PRM is positive the benefits of reoperation always have to be balanced against the risks of this technically demanding procedure. Redo surgery appears to have the most obvious survival advantage in early stage patients, especially when few nodes are involved (N0 or N1)[[56](#_ENREF_56),[57](#_ENREF_57)]. In contrast, advanced N stage patients with positive margins may not benefit from an extended re-excision. Multidisciplinary options, including chemotherapy and radiotherapy, are probably more appropriate treatments for positive-margin patients, especially in patients with bulky node disease[[56](#_ENREF_56),[58](#_ENREF_58)]. This is further supported by a retrospective comparison of the Dutch D1D2 trial where the authors observed significant improvement in survival and local recurrence rates with the use of chemoradiotherapy after a microscopically incomplete R1 resection[[56](#_ENREF_56),[58](#_ENREF_58)].

***Lymphadenectomy in resectable GC***

The extent of lymphadenectomy in the treatment of GC has been debated for more than two decades. The majority of Japanese and Korean (*i.e.*, Eastern) surgeons would agree that an extended lymphadenectomy (D2) leads to improved outcomes and survival. Several large retrospective studies from those groups have illustrated an impressive overall survival, unfortunately not reproduced in most Western series.

Early published studies in the West did not show any advantage in long-term survival of D2 lymphadenectomy as compared to D1 dissection, mainly due to an elevated morbidity and mortality associated with D2 procedure[[59-62](#_ENREF_59)].

As shown in table 4, only a Taiwanese study[[63](#_ENREF_63),[64](#_ENREF_64)] found a significant survival advantage of D2 with respect to D1, while the British[[60](#_ENREF_60),[65](#_ENREF_65)], Dutch[[59](#_ENREF_59),[66](#_ENREF_66)] and Italian[[67](#_ENREF_67),[68](#_ENREF_68)] trials did not find a significant difference in long-term survival comparing the two procedures. The Japanese trial[[69](#_ENREF_69)] did not find any survival advantage of prophylactic para-aortic nodal dissection (PAND).

In contrast Roviello *et al*[[70](#_ENREF_70)] showed that D2 dissection was performed with acceptable mortality and morbidity (2% and 17% respectively) and Siewert *et al*[[71](#_ENREF_71)] found improved survival for stage II patients that underwent D2 lymphadenectomy with no increased morbidity.

More recently, the Dutch GC Group Trial[[32](#_ENREF_32)] showed that, compared with D1, D2 lymphadenectomy was associated with lower local recurrence and lower cancer-related death rates, despite a significantly higher postoperative mortality, morbidity and reoperation rates. The Italian GC Study Group[[67](#_ENREF_67)] randomized 267 patients and compared the short-term results of D1 and D2 lymphadenectomy for curable GC. Pancreaticosplenectomy was not considered as a routine part of the D2 gastrectomy. This study did not show significant differences in operative mortality, morbidity and duration of postoperative hospital stay. The authors concluded that modified D2 lymphadenectomy, spleen-preserving D2 resection technique, currently available in high-volume centers, is a safe option to treat gastric carcinoma of Western patients.

In order to achieve better surgical outcomes Northern Europe countries carried out a centralization and standardization of surgical procedures in GC. In Denmark, this process improved short term results, 30-d hospital mortality has decreased from 8.2% to 2.4% and the proportion of patients with at least 15 lymph nodes removed has increased from 19% to 76%[[72](#_ENREF_72)]. Centralization of GC surgery and/or audits for GC are currently implemented in the United Kingdom, Sweden, Finland, and the Netherlands[[73](#_ENREF_73), [74](#_ENREF_74)].

In conclusion, the current consensus is that for medically fit patients D2 lymphadenectomy should be the standard procedure. It should be carried out in specialized, high-volume centers with appropriate surgical expertise and postoperative care[[75](#_ENREF_75),[76](#_ENREF_76)]. The German, British and ESMO-ESSO-ESTRO guidelines adopted this as the standard of care for surgical treatment with curative intent[[77](#_ENREF_77)].

***Is there a place for laparoscopic gastrectomy?***

Laparoscopic gastrectomy in GC is gaining popularity worldwide as a minimally invasive alternative treatment to traditional open surgery.

Laparoscopic surgery has the potential benefits of a decreased operative morbidity and reduced recovery times but with longer operative time.

Most meta-analyses support these benefits in distal gastrectomy, however, the oncological and long-term outcomes still need to be validated[[75](#_ENREF_75),[76](#_ENREF_76)]. Postoperative morbidity is greater particularly in total gastrectomy. According to the JGCA guidelines, D2 dissection of stations 12a or 10 can be technically demanding due to the risks of organ injury, bleeding, and/or bile and pancreatic leakage. There is also no consensus on the technique of anastomosis following a laparoscopic total gastrectomy. The introduction of a circular stapler with transorally inserted anvil has enable esophago-jejunostomy anastomosis. This procedure resembles conventional approach by laparotomy[[78](#_ENREF_78)].

The most common technique is laparoscopic assisted distal gastrectomy (LADG) without hand assistance, which is also the most frequently reported procedure in the current literature[[79-81](#_ENREF_79)]. Trials are currently ongoing in Japan (JCOG-0912), South Korea (KLASS and KLASS-02) and China to compare open and laparoscopic surgery in EGC[[81](#_ENREF_81),[82](#_ENREF_82)]. These should provide further evidence regarding the role of laparoscopic approach before moving to the laparoscopic treatment of locally advanced GC, especially when a TG with D2 lymphadenectomy is recommended. As such, and at the time of writing this paper, one cannot advice laparoscopic gastrectomy for treating GC, outside a clinical trial.

**TREATING GC ON THE 21st CENTURY: Are we ready for personalized therapy?**

This is certainly an active topic of clinical and basic research not only because GC is a highly prevalent disease but also because the treatments used may be effective but sometimes very toxic[[83](#_ENREF_83)]. Although the prognosis and 5-year survival is still poor for patients with locally advanced GC, a considerable progress has been achieved in the past two decades[[84](#_ENREF_84)]. Besides staging procedures which allow a more accurate staging of the disease enabling a more appropriate selection of patients for pre-operative cytoreductive CT, both surgical and medical therapies have evolved substantially. From a surgical point of view, a modified D2 lymphadenectomy is now the standard procedure for medically fit patients with locally advanced GC in most European Centers. Short and long term results improved substantially in the Western, as long as carried out in specialized, high-volume centers with appropriate surgical expertise and postoperative care. This was certainly a major step towards curative therapy in GC patients in the Western.

Peri-operative CT using ECF as in the MAGIC trial is now standard of care for stages II and III disease as recommended by ESMO-ESSO-ESTRO clinical practice guidelines[[77](#_ENREF_77)]. This was also a major breakthrough if we recall that up to one decade ago CT was not systematically considered part of the curative treatment of GC.

***Host factors responsible for heterogeneity of response***

Although, peri-operative CT followed by radical surgery is now the standard of care for most patients with stage II-III non metastatic GC, less than 50% of patients complete the full protocol due to its toxicity[[27](#_ENREF_27)]. In this respect, there has been recent interest in exploring relationships between body composition, especially proportions of lean and fat tissues with treatment toxicities. The most recent definition of cancer cachexia specifically involves depletion of muscle mass, which sometimes may not impact on body weight. As shown on figure 1, patients may become sarcopenic despite a normal or even high body mass index. Muscle depletion is characterized both by a reduction in muscle size and increased proportion of inter- and intramuscular fat. Fat infiltration given by muscle attenuation (MA) is a further manifestation of the wasting process (Figure 1).

Prado *et al*[[85](#_ENREF_85)] observed that in metastatic breast cancer patients receiving capecitabine treatment, sarcopenia was a significant predictor of toxicity and time to tumor progression. The authors reported a 28-fold increase in the relative risk of grade 3 and 4 neutropenia if a patient lean body mass (LBM) was < 89% of age and sex-adjusted norms. They hypothesize that this relationship was primarily due to a pharmacokinetic effect as fat-free mass (LBM plus bone tissue) and total body water were better predictors of 5-FU pharmacokinetics (clearance and volume of distribution) that body surface or body weight. This has also been reproduced in patients with metastatic lung and pancreatic cancer[[86](#_ENREF_86)]. Sarcopenia has also been associated with unfavorable clinical outcomes such as increased length of hospital stay, increased incidence of infections for hospitalized patients, and mortality in surgical patients[[87](#_ENREF_87)]. Lieffers *et al*[[87](#_ENREF_87)] observed that in patients aged more than 65 years operated for colorectal cancer, sarcopenia was an independent predictor of both infection and rehabilitation care and, consequently, a longer length of hospital stay. Finally, it is important to stress that imaging of sarcopenia can be done using the CT scan performed at the time of routine imaging studies for tumor evaluation and/or restaging[[88](#_ENREF_88)], as long as the appropriate software is available as shown on Figure 2.

It would then be interesting to test whether these observations of body composition, muscle mass measurement and CT toxicity, also hold true in respect to patients with advanced GC selected to perioperative CT followed by radical surgery. This could shed some light on the issue why patients do not benefit equally from these treatment options.

***Analysis of TUMOR FACTORS which might allow a more personalized therapy***

Inter-individual variability of drug response or resistance may also be related to tumor heterogeneity. The identification of predictive tumor markers at the time of diagnosis would also allow for stratifying patients to more effective treatments, as current therapeutic strategies do not uniformly benefit all patients. Although very toxic in some patients, one cannot forget that complete pathologic responses are being reported with increasing frequency[[89](#_ENREF_89)] thus making the identification of these predictive factors mandatory.

In a recent study, the authors found that pathologic complete response was observed in 20% (10/50) of patients and a further 20% (10/50), achieved near complete histological remission (< 10% residual tumor). Among these very good responders, 85% (17/20) had intestinal type tumors, 10% (2/20) had diffuse and 5% (1/20) had mixed type tumors[[89](#_ENREF_89)].

In regard to molecular markers, and similarly to what occurs in colorectal cancer[[90](#_ENREF_90)], MSI status seems to affect both the prognosis and the response to 5-FU based chemotherapies. One study found 5-FU based adjuvant chemotherapy prolonged disease-free survival in patients with GC stage II and III disease only in patients with tumors MSS or MSI-low, in contrast with the MSI-high group who did not seem to benefit from this type of therapy[[91](#_ENREF_91)]. However, these are conflicting data as another study did not find that MSI status significantly affected response to 5-FU CT[[92](#_ENREF_92)].

Current research is thus focusing on identifying cancer biomarkers, which will elucidate treatment response and drug resistance mechanisms[[93](#_ENREF_93)]. Real progress will only be achieved through the development of new treatment options that have reduced cell toxicity compared with that of standard therapeutic regimens. Nowadays, except for the status of human epidermal growth factor-2 (HER2) which is used to guide trastuzumab therapy, no other biomarkers are used in clinical practice.

Considering the amount of effort that has been put in clarifying the pathogenesis of GC, we are now hoping that these new discoveries will lead to the translation of these insights into the clinical arena. New proteomic technologies which promote large-scale sample screening will hopefully open new avenues for targeted and personalized therapies in patients with GC[[94](#_ENREF_94)]. As much as unraveling gastric carcinogenesis seems closer and closer, concepts such as the migrating cancer stem cell remind us that this enigma is still faraway from being solved. Faraway, so close!

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**Table 1 Randomized trials of surgery with and without neoadjuvant or perioperative chemotherapy in resected gastric cancer**

|  |  |  |  |
| --- | --- | --- | --- |
| **Ref.** | **n** | **Chemotherapy** | **Hazard ratio for survival (95%CI)** |
| Cunningham *et al*[27], 2006 | 503 | ECF | 0.75 (0.60-0.93) |
| Ychou *et al*[49], 2011 | 224 | PF | 0.69 (0.50-0.95) |
| Schuhmacher *et al*[28], 2010 | 144 | PF | No significant survival difference |

ECF: Epirubicin/cisplatin/ 5-fluorouracil; PF: Cisplatin/5-fluorouracil.

**Table 2 Randomized trials of adjuvant chemo or chemoradiotherapy in resected gastric cancer**

|  |  |  |  |
| --- | --- | --- | --- |
| **Ref.** | ***n*** | **Regimen** | **3Y Disease free survival rate (%; *P-*value)** |
| Lee *et al*[41], 2012 | 458 | XP *vs* XP/XRT/XP | No significant Disease free survival difference |
| Yu *et al*[45], 2012 | 68 | 5FU/LV *vs* 5FU /LV/RT | 44.1 *vs* 67.7 (*p* < 0.05) |
| Kim *et al*[44], 2012 | 90 | 5FU/LV *vs* 5FU/LV/RT | No significant Disease free survival difference |
| Kwon *et al*[46], 2010 | 61 | 5FU/LV *vs* 5FU/LV/RT | No significant Disease free survival difference |
| Bamias *et al*[43], 2010 | 147 | DP *vs* DP/RT | No significant Disease free survival difference |

X: Capecitabine; 5-FU: 5-fluorouracil; LV: Leucovorin; P: Cisplatin; D: docetaxel; RT: Radiotherapy (45 Gy).

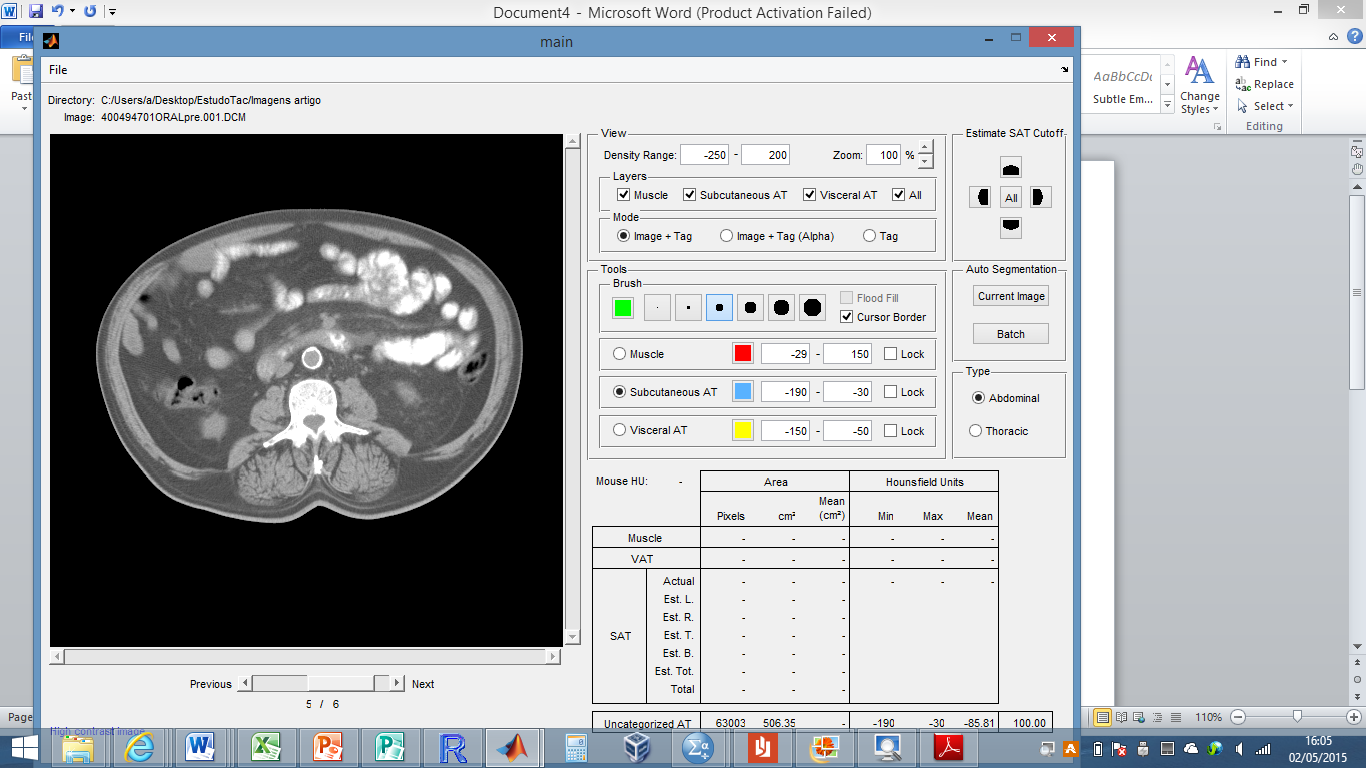
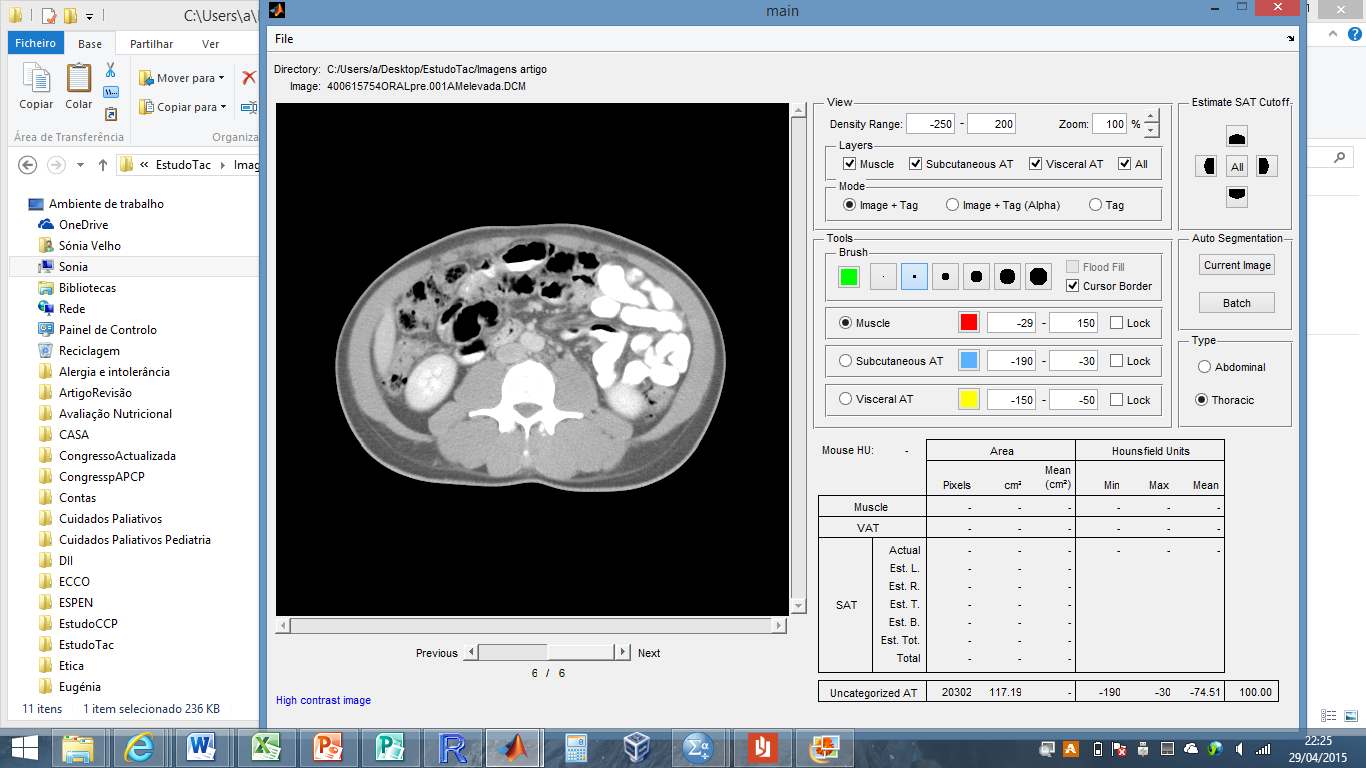
**Table 3 Criteria for adequate surgical margins**

|  |  |  |
| --- | --- | --- |
|  | **German S3** | **JGCA** |
| Resection margins | Oral, aboral  circumferential | Proximal |
| Proximal resection margins | 5 cm (intestinal type)  8 cm (difuse type) | -cT1: 2 cm  -cT2-T4 :  3 cm (expansive)  5 cm (infiltrative) |

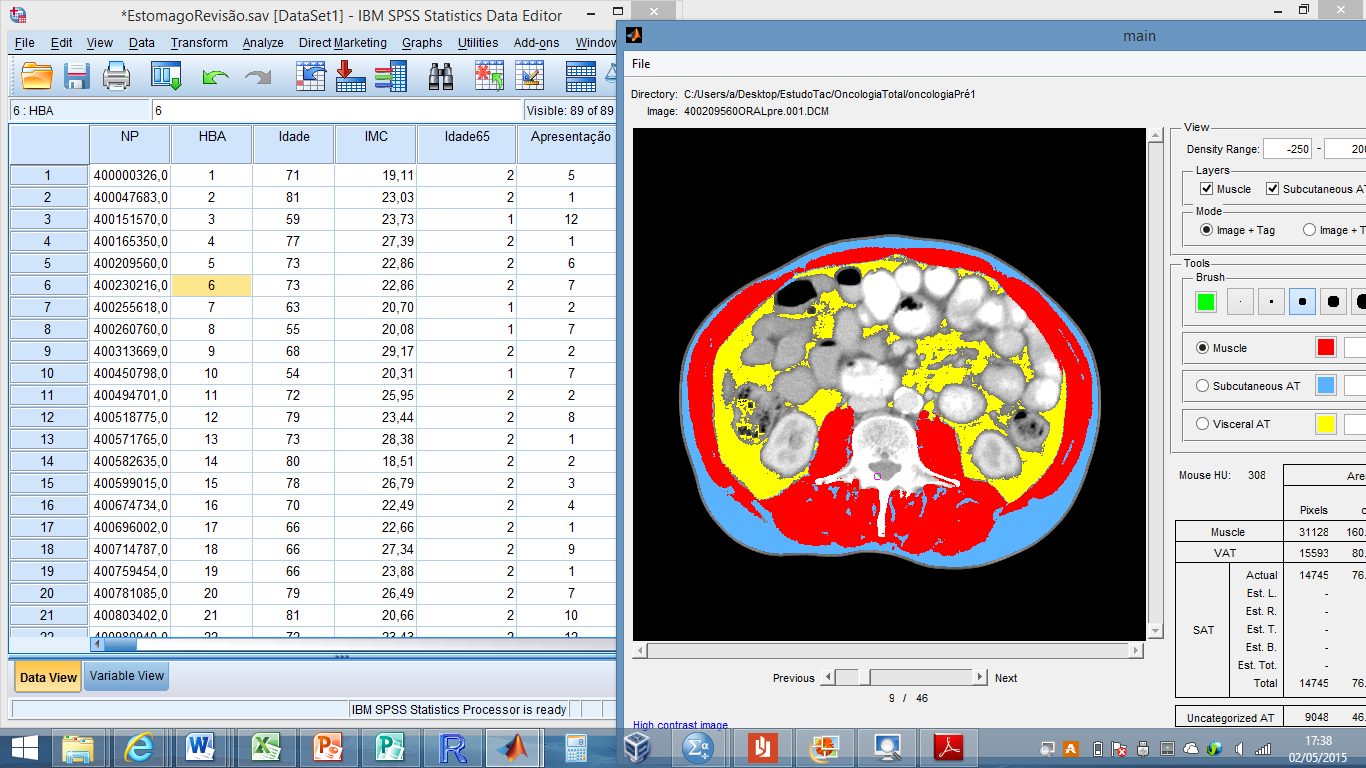
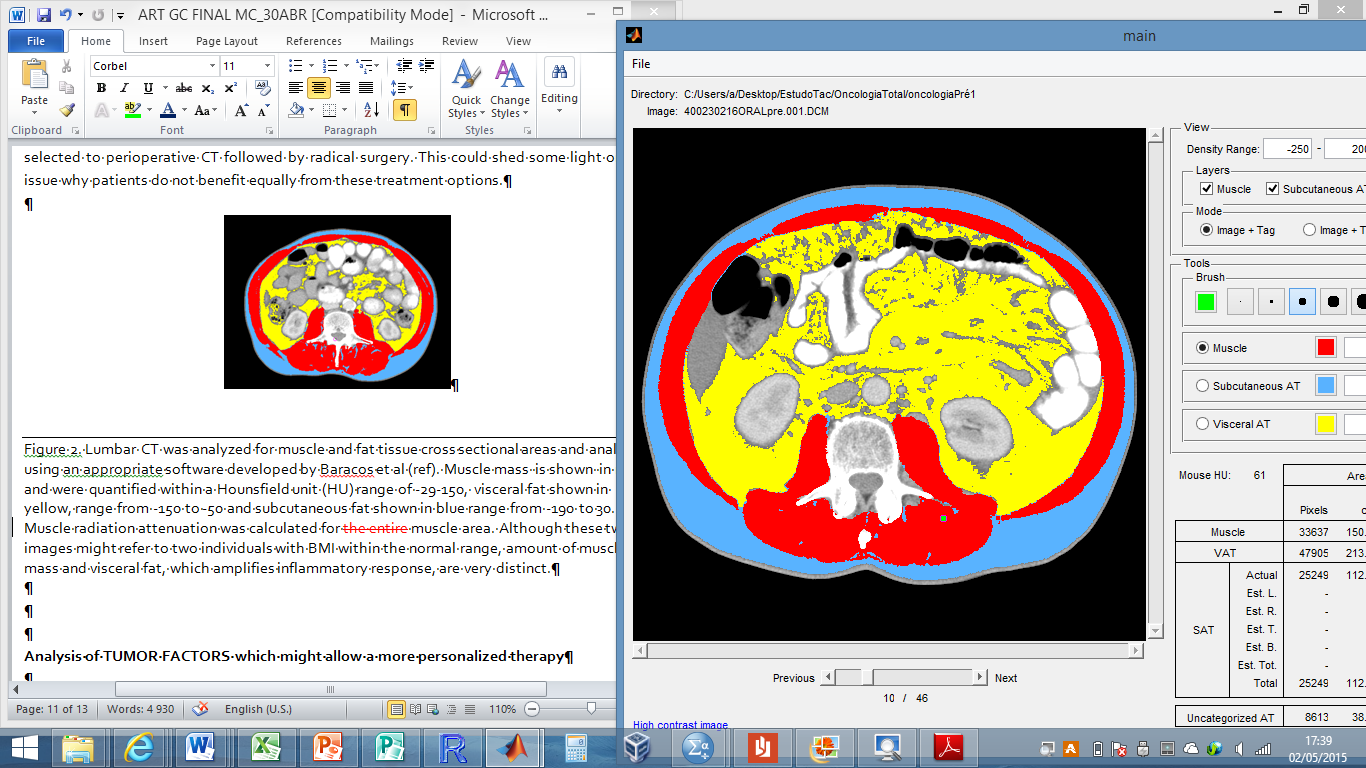
**Table 4 Selected randomized controlled trials studying the extent of the Lymph node dissection for patients with gastric cancer**

PAND: paraaortic node dissection.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Year published** | **Region** | **Extent of Lymph node dissection** | **Patients**  **(*n*)** | **Morbidity**  **(%)** | **Mortality (%)** | **5-yr overall survival (%)** |
| Dent  *et al*[62] | 1988 | South Africa | D1  D2 | 22  21 | 22  43 | 0  0 | N/A  N/A |
| BonenKamp  *et al*[59,66] | 1995 | The Netherlands | D1  D2 | 380  331 | 25  43 | 4  10 | 45  47 |
| Cuschieri  *et al*[60,65] | 1996 | Europe | D1  D2 | 200  200 | 28  46 | 6.5  13 | 35  33 |
| Wu  *et al*[63,64] | 2004 | Taiwan | D1  D3 | 110  111 | 7.3  17.1 | 0  0 | 53.6  59.5 |
| Sasako  *et al*[69] | 2008 | Japan | D2  D2 + PAND | 263  260 | 20.9  28.1 | 0.8  0.8 | 69.2  70.3 |
| Degiuli  *et al*[67,68] | 2010 | Italy | D1  D2 | 133  134 | 12  17.9 | 3  2.2 | 66.5  64.2 |
|  | | | | | | | |



**Figure 1 Axial computed tomography images of the third vertebra region.** Paraspinal muscles are clearly different between the two subjects as is mesenteric fat and fat infiltrating muscle – muscle radiation attenuation. Low relative muscularity and expanded visceral fat are associated with increased toxicity and decreased survival.

**Figure 2 Lumbar computed tomography was analyzed for muscle and fat tissue cross sectional areas and analyzed using an appropriate software developed by Baracos *et al* (ref).** Muscle mass is shown in red and were quantified within a Hounsfield unit (HU) range of -29-150, visceral fat shown in yellow, range from -150 to -50 and subcutaneous fat shown in blue range from -190 to 30. Muscle radiation attenuation was calculated for muscle area. Although these two images might refer to two individuals with the same body mass index (23 kg/m2) and age (73 years), amount of muscle mass and visceral fat, which amplifies inflammatory response, are very distinct.