Gastric cancer : staging, treatment, and surgical quality assurance

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CHAPTER 17

General discussion and summary

GENERAL DISCUSSION

Gastric cancer is the second leading cause of cancer death worldwide, affecting approximately one million new individuals per year.[1] Highest incidence rates are described in Northeast Asia, Eastern Europe, and much of the east part of South America, while Europe and North America are low incidence areas.[2] Survival in the Western world is dismal, with five-year survival rates for all patients with gastric cancer of approximately 25%, both in Europe and the United States.[3,4] In the Netherlands, approximately 1,800 patients are diagnosed with gastric cancer each year, and five-year survival is 22%.[5]

STAGING

Cancer staging is one of the fundamental activities in oncology.[6,7] For over 50 years, the TNM classification has been a standard in classifying the anatomic extent of disease.[8] In order to maintain the staging system relevant, the International Union Against Cancer and the American Joint Committee on Cancer (AJCC) have collaborated on periodic revisions of this staging system, leading to the 7th edition in 2010.[9] With each staging system revision, there is a tension between improving prognostic value of the staging system by adding subdivisions of existing stage groupings and introducing new predictive parameters, and the desire to keep the staging system simple. With an increasing number of categories for the 7th edition gastric cancer staging system, it has become more complex, while predictive accuracy has not improved. Increasing the number of categories of the staging system is not unique to gastric cancer.[9] With the growing availability of pathologic and molecular data, there is a trend towards incorporating more and more information into newer staging systems. Although these new categories might better reflect the natural history and prognosis of these diseases, there is a limit to the improvement of prognostic accuracy achievable with a categorical anatomic-based staging system like the TNM-classification.[10,11] At the same time, the goal of creating an intuitive, easy to use staging system disappears, and in daily clinical practice, cancer staging consists of using complex tables.

Meanwhile, tools for individual patient prognostication have been developed that significantly outperform the TNM-classification in prognostic accuracy. For gastric cancer, a nomogram has been developed based on a single US-institution database,[12,13] and has been validated in several international patient cohorts.[14-16] The question is if the TNM-classification should aspire to the same goal of highly accurate individual patient prognostication as these nomograms. Prognostication is only one of the five goals of the TNM-classification, and all other goals are directed towards a simple intuitive international language: to aid the clinician in planning and evaluating treatment, to facilitate the exchange of consistent information, and to contribute to research.[6]

SURGERY

Shortly after finishing accrual of the Dutch Gastric Cancer Group trial comparing D1 (limited) with D2 (extended) lymphadenectomy, morbidity and mortality results were published indicating a significantly higher mortality after a D2 dissection (10% versus 4%),[17] similar to the Medical Research Council Gastric Cancer trial.[18] The number of splenectomies and pancreatic tail resections, which have shown to increase postoperative mortality, was also higher in the D2 group. Analyses performed after 11 and 15 years of follow-up revealed no significant differences in overall survival.[19,20] However, gastric-cancer related death at 15 years was significantly lower after a D2 (37%) when compared to a D1 (48%) dissection ($P = 0.01$),[20] suggesting that when postoperative mortality can be avoided, a D2 lymphadenectomy improves survival compared to a D1 lymph node dissection. In a more recent, Italian study, a D1 versus D2 lymphadenectomy was analyzed in 267 patients treated in five centers.[21] Although long-term survival results have to be awaited, and the study population might be too small to detect differences in overall survival, postoperative mortality after a D2 dissection was only 2.2%. This taken together with the currently performed spleen-preserving gastrectomy indicates that a D2 lymph node dissection in experienced centers should be the recommended type of surgery in advanced gastric cancer, not only in Asia, but also in Europe and the United States.[22,23] A routine pancreatic tail and spleen resection should be avoided.[24]

Although laparoscopic surgery has been applied for gastric cancer for over two decades, only a limited number of randomized controlled trials on this subject have been reported.[25-29] A recent review on these randomized studies indicates that laparoscopic gastrectomy is safe and feasible, and that short term outcomes are better than those of open gastrectomy in patients with early gastric cancer.[30] Large multicenter randomized controlled trials are necessary to establish the role of laparoscopy in the treatment of gastric cancer. As the learning curve for laparoscopic gastrectomy takes at least 60 operations, laparoscopic gastrectomy should not be performed in low-volume hospitals.[31]

SURGICAL QUALITY ASSURANCE

Improving quality of care for patients with resectable gastric cancer is a major challenge, especially when performed in lower volume centers like in many European countries. Whereas Japan has established national screening programs for gastric cancer, and has a two to seven-fold higher incidence rate as compared to European countries, in Europe incidence rates are relatively low leading to lower exposure of hospitals to patients with resectable gastric cancer.

Although randomized controlled trials provide important information on the optimal treatment strategy for gastric cancer, and trials in general can improve outcomes on a national level, the majority of patients are treated outside the framework of clinical trials. Especially improvements in the structure and process of care on a nationwide level will bring benefit to this group of patients. National quality assurance programs aim to

reduce variations between providers of care and to improve outcomes after gastric cancer surgery. The most frequently used quality assurance programs include centralization of care to high-volume or high-quality hospitals and clinical auditing.

Luft et al. were the first to publish on the relation between hospital volume and outcomes.[32] More than 20 years later, Birkmeyer et al. published another landmark study showing a relation between increasing hospital volume and lower postoperative mortality for several surgical procedures.[33] Ever since, a large number of studies on the effect of hospital volume on both short term and long term outcomes after gastrectomy has been published, and in the majority of these studies, a significant relation between high hospital volume and better outcomes was found.[33-48]

In Denmark, the available evidence on a volume-outcome relationship has led to enforced centralization of gastric cancer surgery from 37 to 5 hospitals as of 2003, which has resulted in a significant decrease in postoperative mortality (8.2% in 2003 to 2.4% in 2008, $P < 0.05$), and an increase in the number of patients with at least 15 lymph nodes examined (19% - 67%).[37] Centralization of gastric cancer surgery is currently implemented in the United Kingdom, Sweden, Finland, and as of 2012 in the Netherlands. As esophagectomies have already been centralized in the Netherlands, esophagogastric cancer surgery will be centralized towards centers currently performing esophagectomies, resulting in upper GI centers. This enables the formation of dedicated upper GI surgical and multidisciplinary teams, and eliminates the possibility that patients with incorrectly staged junctional tumors need to be transferred from an esophageal to a gastric cancer center or vice versa after first surgical inspection of the tumor.

Meanwhile, using hospital volume as the sole basis for referral to improve outcomes is criticized.[33] Although hospital volume can be used to identify groups of hospitals with better outcomes on average, individual low volume hospitals can have excellent outcomes and vice versa. In contrast to volume-based referral, outcome based-referral avoids this problem, and has proven its value for esophagectomy in the Western part of the Netherlands. In this region, a prospective audit was conducted to identify hospitals with excellent performance in esophagectomy. During the five-year audit, a gradual concentration towards centers with excellent performance occurred, leading to a drop in postoperative mortality (12% to 4%) and an improvement in survival.[49] Others have advocated the identification of processes associated with excellent outcomes, and to implement these in low volume hospitals, rather than to refer patients to centers of excellence. However, identification of these processes and determination of their impact on quality of care remains challenging.[50]

It has been suggested that centralization combined with auditing is more effective when compared to centralization alone.[51] With auditing, providers of care are monitored and their performance is benchmarked against their peers. Data is usually entered by the providers of care and is centrally collected. A disadvantage of auditing is the effort needed to collect the data. Information technology solutions incorporated in electronic

medical record systems are needed to solve this problem. In the United Kingdom, a national esophagogastric cancer audit was initiated in 2002 by the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland.[52] In the United States, the National Surgical Quality Improvement Program is used to audit many different surgical procedures, and several studies have shown a decrease in postoperative morbidity and mortality for vascular and general surgical procedures after introduction of this audit.[53-55] Sweden also has a long tradition of clinical auditing, which started with the Swedish Rectal Cancer Registry, but is now extended to upper-GI surgery.[56] In the Netherlands, as of 2011, the Dutch Upper-GI Cancer Audit has started, with the aim of capturing all esophageal and gastric cancer resections in the Netherlands, and to provide weekly feedback to participating surgeons. Surgeons from several European countries are currently collaborating on the development of a European Upper GI Cancer Audit (EURECCA Upper GI).

MULTIMODALITY TREATMENT

Whereas Asian patients mainly receive postoperative chemotherapy with S-1, in the Western world postoperative chemoradiotherapy or perioperative chemotherapy are administered. Due to differences in patient selection, it is not possible to compare results from the Intergroup 0116 study on postoperative chemoradiotherapy with results from the MAGIC study on perioperative chemotherapy.[57,58] However, it becomes clear that the toxicity profile of the multimodality regimen is crucial for both the patient to complete therapy, and for the trial to finish accrual. As preoperative therapy is generally associated with improved compliance without compromising resectability,[59] this should be the recommended therapy for patients with advanced, resectable gastric cancer. After radical surgery, postoperative therapy should be administered when tolerated by the patient, but no standard regimen for this has been established. In case of contaminated resection margins (R1 resection), locoregional disease is left behind and postoperative chemoradiotherapy should be the recommended therapy.[60] Patients with distant micrometastases will benefit from postoperative chemotherapy, but no diagnostic modality can identify these metastases so far, and therefore, the regimen of choice remains unclear. To address this issue, the Dutch CRITICS study was initiated in 2008.[61] In this study, all patients receive three cycles of preoperative ECC, followed by gastrectomy with D1+ surgery (i.e. an extended lymphadenectomy without the lymph nodes in the splenic hilus and without a spleen and pancreatic tail resection). Then patients in arm A receive another three cycles of ECC, while patients in arm B receive postoperative CRT with cisplatin, capecitabine, and 45 Gy radiotherapy. An estimated 788 patients are required for this study; currently over 400 patients from the Netherlands, Sweden, and Denmark are included.

Another, recent development is the use of the monoclonal antibody trastuzumab for HER2 positive gastric cancers, which account for approximately 30% of all gastric

cancers.[62] In the large, international ToGA trial, a significant benefit in overall survival was found for patients with inoperable locally advanced or recurrent HER2 positive gastric cancer receiving trastuzumab versus conventional chemotherapy. Currently, in many trials the use of trastuzumab in HER2 positive resectable gastric cancer is investigated, but no results have been published so far. However, there is debate on the currently accepted diagnostic methods to detect HER2 positive tumors.[63,64] In contrast to breast cancers, gastric cancers are highly heterogeneous, and HER2 expression is different throughout the tumor. Furthermore, a considerable number of tumors in the ToGA trial were negative by immunohistochemistry, which is the diagnostic modality used in daily clinical practice, but showed HER2 gene amplification with FISH, which is the gold standard. Therefore, more research is needed on the diagnosis of HER2 expression in gastric cancer in order to accurately interpret data from currently accruing clinical trials.

CONCLUSIONS AND FUTURE PERSPECTIVES

Cancer staging represents a compromise in accounting for the most prognostically relevant factors to aim at a simple, intuitive, useful, common language to describe the natural history of a tumor. It should not be confused with more complex, multivariable prognostication models, which may be useful in defining groups of patients at homogenous risk of recurrence, regardless of anatomic TNM characteristics. Future TNM classifications for gastric cancer should aspire more simplicity and should aim for a clinically more useful staging system.

Surgery is the only potentially curative treatment for gastric cancer, and despite recent developments in multimodality therapy it remains the cornerstone of treatment. A gastrectomy with D2 lymphadenectomy without routine spleen and distal pancreatic resection is the recommended type of surgery for advanced, resectable gastric cancer. The current debate focuses on the question which multimodality treatment schedule should be administered to patients with resectable gastric cancer. Because of the higher compliance of preoperative therapy when compared to postoperative therapy, preoperative chemotherapy should be recommended for all patients with advanced gastric cancer, followed by either postoperative chemotherapy or chemoradiotherapy, an issue currently addressed in the international CRITICS trial.

Further tailoring of treatment based on a patient's genetic profile has been pursued. However, HER2, which is the most promising genetic marker so far, has been subject to critique due to the intratumoral heterogeneity of HER2 expression in gastric cancers and discrepancies between IHC and FISH results for HER2 testing, thereby impeding an accurate assessment of HER2 status. Truly clinically useful genetic markers for gastric cancer remain to be awaited.

Another approach to tailor made treatment is practiced in Japan. Due to the high caseload of patients, Japanese surgeons and gastroenterologists have the opportunity to differentiate treatment based on clinical tumor stage. More experience with endoscopic

techniques, including endoscopic (sub)mucosal dissection, high volume and laparoscopic surgery, and the use of a preoperative sentinel node procedure provide a level of care for gastric cancer patients far beyond that in most Western centers.

Because gastric cancer surgery in the Western world is associated with high postoperative mortality, and patients presenting with gastric cancer become older and have an increasing number of comorbidities, gastric cancer resections should be performed in centers with sufficient experience. Although in the Netherlands, several regional initiatives were started to centralize gastric cancer care, nationwide programs are needed to improve care for all gastric cancer patients. The proposed minimal hospital volume standards of 10 per year in 2012 and 20 per year as of 2013 for gastric cancer resections are a first step towards this improvement. With this centralization of surgery, it is expected that postoperative 30-day mortality for the annual 500 gastric cancer resections in the Netherlands will decrease from the current 8% to below 5%, saving the lives of approximately 15 patients annually in the perioperative period. But the available evidence also confirms that long-term survival will improve with referral of gastrectomies towards high volume centers.

However, surgical excellence in the treatment of gastric cancer not only requires expertise in gastrectomies, but also in other upper gastrointestinal surgery, including esophagectomies. Only with the formation of 'upper GI centers' it is possible to adequately treat patients with junctional tumors and patients with complex gastric cancers. Furthermore, expertise should not be limited to the surgical treatment of these cancers. Rather, experience should be present in the whole multidisciplinary chain involved in treating gastric cancer, including diagnostic imaging, upper GI endoscopy and endoscopic ultrasound, surgery, perioperative care, intensive care, nutritional support, chemotherapy, and radiotherapy. Therefore, it should be encouraged that the Dutch Upper GI Cancer Audit (DUCA), which is currently a monodisciplinary surgical audit, will expand to all disciplines involved in esophagogastric cancer care, thus also capturing patients who are never considered for surgery. As the DUCA has started in 2011, and only 60% of all gastrectomies in the Netherlands were registered in the first registration year, comparing quality of care between participating hospitals is not yet possible. But when case ascertainment will increase over the years and centralization of gastrectomies will take place, in the near future the DUCA will be an instrument to identify centers of excellence which can share their best practice with other hospitals in the Netherlands. Collaboration with other upper GI audits in Europe, which is currently under way in the EURECCA Upper GI consortium, will provide the opportunity to share knowledge with other countries and define best practice throughout Europe. Bringing together this international high quality data will also enable the development of refined treatment algorithms for specific subgroups of patients, for example the elderly. Ultimately this will lead to the optimal choice of treatment for every gastric cancer patient in Europe.

SUMMARY

Research described in this thesis focuses on several aspects of gastric cancer care: staging and prognostication, multimodality treatment, and surgical quality assurance.

PART I - STAGING AND PROGNOSTICATION

Cancer staging is one of the fundamental activities in oncology.[6,7] For over 50 years, the TNM classification has been a standard in classifying the anatomic extent of disease.[8] In order to maintain the staging system relevant, the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) have collaborated on periodic revisions of this staging system, leading to the 7th edition in 2010.[65] In **Chapter 2**, differences between the 6th and 7th edition TNM classification for gastric cancer are described, and both staging systems are compared with regards to complexity and predictive accuracy. In the 7th edition TNM classification, nodal status cut-off values were changed, leading to a more even distribution for the redefined nodal classification groups. This increased the predictive accuracy of N-classification. Overall, the TNM staging system became more complex, with an increase in the number of TNM groupings from 56 to 80, which did not result in an increased predictive accuracy. Future refinements of the TNM-classification should consider whether increased complexity is balanced by improved prognostic accuracy.

Another change that was incorporated in the 7th edition TNM classification was the addition of tumor grade as an independent determinant of stage grouping in early stage tumors. With the significantly lower prognosis of poorly differentiated early stage adenocarcinomas, these tumors might become candidate for neoadjuvant therapy, given an accurate identification of these tumors with preoperative staging. In **Chapter 3**, the accuracy of preoperative histopathologic grading in adenocarcinomas of the gastroesophageal junction (GEJ) was evaluated. The overall accuracy of tumor grade assessment was 73%. However, in early stage tumors the sensitivity to detect a poorly differentiated tumor was only 43%, and 21% of patients with an early stage GEJ tumor were assigned to an incorrect stage/prognostic group based on preoperative tumor grading. Caution should therefore be exhibited in staging patients with esophageal adenocarcinoma based on preoperative biopsy data.

Although the TNM classification can be used to assess a patient's prognosis, tools for individual patient prognostication have been developed that significantly outperform the TNM-classification in prognostic accuracy. For gastric cancer, a nomogram has been developed based on a single US-institution database,[12,13] and has been validated in several international patient cohorts.[14-16] **Chapter 4** describes the development of a new gastric cancer nomogram that not only can predict survival for patients directly after an R0 gastrectomy, but also for patients alive at time points after surgery. This conditional probability of survival nomogram was highly discriminating (concordance index: 0.772), and surviving one, two, or three years from surgery showed a median improvement of

5-year disease-specific survival of 7.2%, 19.1%, and 31.6%, as compared to the baseline prediction directly after surgery. This nomogram was based on variables available directly after surgery, while variables available with follow-up (such as weight loss and performance status) did not further improve the predictive accuracy of this nomogram.
In **Chapter 5**, the performance of the original gastric cancer nomogram, which was based on patients who underwent surgery without multimodality therapy, was assessed in a group of patients who received postoperative chemoradiotherapy after an R0 resection for gastric cancer. The nomogram significantly underpredicted 5-year survival for patients who received postoperative chemoradiotherapy, indicating a benefit in survival for patients who receive postoperative chemoradiation after an R0 resection for gastric cancer. Furthermore, this study stresses the need for updating nomograms that incorporate multimodality therapy use.

PART II - MULTIMODALITY TREATMENT

Over the past decade, many trials have been performed in which the effect of multimodality treatment on survival for resectable gastric cancer was evaluated. In **Chapter 6**, an overview of the literature on the treatment of gastric cancer is presented, and the available multimodality strategies are discussed. Currently accepted regimens include postoperative monochemotherapy with S-1 in Asia,[66] and perioperative chemotherapy and postoperative chemoradiotherapy in the Western world.[57,58]
In **Chapter 7**, patterns of recurrence and survival of patients who received postoperative chemoradiotherapy were compared to recurrence and survival patterns of patients who only underwent surgery. The local recurrence rate was significantly lower in the chemoradiotherapy group (5% versus 17%, $P = 0.0015$). Subgroup analysis revealed that this difference was even stronger in patients who underwent a gastrectomy with a limited (D1) lymph node dissection (2% versus 18%, $P = 0.001$), while no difference was found for patients who underwent an extended (D2) lymph node dissection. Additional analysis with prolonged follow-up showed a higher 2-year overall survival for patients who received postoperative chemoradiotherapy after a D1 lymphadenectomy compared to surgery alone, and no difference in overall survival for patients who received a D2 dissection. Postoperative chemoradiotherapy was also significantly associated with higher two-year overall survival for patients who underwent a microscopically irradical (R1) resection (66% versus 29%, $P = 0.02$). Results from this study indicate that, especially after a gastrectomy with a limited lymph node dissection, postoperative chemoradiotherapy has a major impact on local recurrence and overall survival. Postoperative chemoradiotherapy should be offered to patients who undergo a microscopically irradical (R1) resection.
In **Chapter 8**, the results of a study on lymph node yield after gastric cancer resections are described. While it is suggested that more than 15 lymph nodes (LNs) should be evaluated for accurate staging of gastric cancer, LN yield in Western countries is generally low. The effect of preoperative chemotherapy on LN yield in gastric cancer is unknown. In this

study, LN yields of patients who received preoperative chemotherapy and patients who only underwent surgery were compared. Preoperative chemotherapy was not associated with a decrease in LN yield, indicating that evaluating more than 15 LNs after gastrectomy is feasible, also after administration of preoperative chemotherapy.

In **Chapter 9**, the final chapter of part II of this thesis, the study protocol of the currently accruing Dutch-Swedish-Danish CRITICS trial is described. This trial was initiated to determine which of the two currently used standard regimens for the multimodality treatment of gastric cancer in the Western world, postoperative chemoradiotherapy, or perioperative chemotherapy, should be preferred. In this trial, all patients receive three cycles of preoperative ECC (epirubicin, cisplatin, and capecitabine), followed by D1+ surgery (D2 dissection without splenectomy or pancreatectomy). Postoperative therapy consists of another three cycles of ECC, or chemoradiotherapy with capecitabine and cisplatin without epirubicine. Results of this study will play a key role in the future management of patients with resectable gastric cancer.

PART III - SURGICAL QUALITY ASSURANCE

As an introduction to part III of this thesis, in **Chapter 10**, the results of a systematic review of the literature on quality of care indicators for gastric cancer surgery are described. The availability of specific literature on quality of care indicators was limited, but several indicators could be identified in more general literature on gastric cancer surgery. High hospital volume was found to be strongly related to lower postoperative mortality and higher long-term survival. Several quality indicators regarding operative technique were identified, including the performance of an extended lymphadenectomy, avoiding a routine spleen and pancreatic tail resection, and the use of a pouch reconstruction. Free resection margins were also associated with improved long-term survival.

In **Chapter 11** and **Chapter 12**, incidence and survival patterns for tumors of the esophagus, GEJ, and stomach in the Netherlands over the past 20 years are described. While the incidence of esophageal adenocarcinoma has doubled, the incidence of both tumors of the GEJ and stomach has decreased. These findings most likely reflect true changes in disease burden, rather than being the result of changes in diagnosis or reclassification. The increasing incidence of esophageal adenocarcinoma can be attributed to the increasing incidence of obesity and gastroesophageal reflux disease.[67,68] Over the study period, five-year survival for non-metastatic esophageal cancer strongly improved (12% to 25% for adenocarcinoma, 12% to 19% for squamous cell carcinoma), while five-year survival for non-metastatic GEJ cancer (20%) and stomach cancer (32%) remained stable.

In **Chapter 13**, patterns of care for gastric cancer in the Netherlands over the past 20 years are described. Whereas resection rates for stage I-III gastric cancer have remained stable at about 85%, the use of preoperative and/or postoperative chemotherapy has strongly increased since 2005. In 2008, nearly 40% of the patients with stage I-III gastric cancer received preoperative or postoperative chemotherapy with curative intent, and it is likely

that since then, this percentage has further increased.

In **Chapter 14**, the results of a study on hospital volumes, mortality, and long-term survival for esophagogastric cancer surgery in the Netherlands between 1989 and 2009 are described. In the Netherlands, a minimum hospital volume standard of at least 10 esophagectomies per year was introduced in 2006, while during the study period, no such standard was present for gastrectomies. During the study period, esophagectomy was effectively centralized in the Netherlands, and in 2009, 64% of all esophagectomies were performed in annual volumes of ≥21/year. Gastrectomy has not been centralized, and in 2009 only 5% of all gastrectomies were performed in annual volumes of ≥21/year. Whereas short-term and long-term survival after esophagectomy and gastrectomy improved over the years, this improvement was significantly stronger for esophagectomy. High hospital volume was associated with lower 6-month mortality (HR 0.48, $P < 0.001$) and longer 3-year survival (HR 0.77, $P < 0.001$) after esophagectomy, but not after gastrectomy. However, for gastrectomy, the number of high volume resections in the current study was too low to detect a statistical significant difference in outcomes when compared with low volume resections. This study indicates an urgent need for improvement in the treatment of resectable gastric cancer in the Netherlands.

Chapter 15 describes the results of a study on the effect of hospital type on outcomes after esophagectomy and gastrectomy in the Netherlands. Hospitals were categorized into university hospitals, teaching non-university hospitals, and non-teaching hospitals. Three-month mortality after esophagectomy in university hospitals was 2.5%, compared to above 4% in non-university hospitals ($P = 0.006$). After gastrectomy, three-month mortality was 4.9% in university hospitals, and 8.7% in non-university hospitals ($P < 0.001$). Both after esophagectomy and gastrectomy, three-year survival was higher in university hospitals compared to non-university hospitals. No differences in mortality or survival were found between teaching and non-teaching non-university hospitals. However, when analyzing differences between individual hospitals, there were non-university hospitals with excellent outcomes. Therefore, it can be concluded that centers of excellence can not be designated solely by hospital type, and that detailed information on case-mix and outcomes is needed to identify centers of excellence.

In **Chapter 16**, the results of an international study on esophagogastric cancer surgery between 2004 and 2009 in several European countries are described. Differences in resection rates, postoperative mortality, survival and hospital volumes were compared between the Netherlands, Sweden, Denmark, and England. In the Netherlands, postoperative mortality was average after esophagectomy (4.6%), but significantly higher after gastrectomy (6.9%) when compared to the other countries. Although increasing hospital volume was associated with lower 30-day mortality both after esophagectomy and gastrectomy, differences in outcomes between countries could not just be explained by existing differences in hospital volumes. To further investigate the differences in outcomes, a European upper GI audit is currently initiated.

REFERENCES

1 Kamangar F, Dores GM, Anderson WF. *Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world.* J Clin Oncol 2006;24:2137-2150.

2 Yamaoka Y, Kato M, Asaka M. *Geographic Differences in Gastric Cancer Incidence Can be Explained by Differences between Helicobacter pylori Strains.* Internal Medicine 2008;47:1077-1083.

3 Sant M, Allemani C, Santaquilani M, Knijn A, Marchesi F, Capocaccia R. *EUROCARE-4. Survival of cancer patients diagnosed in 1995-1999. Results and commentary.* Eur J Cancer 2009;45:931-991.

4 SEER Cancer Statistics Review, 1975-2006. National Cancer Institute. Bethesda, MD, 2009. (Accessed at http://seer.cancer.gov/csr/1975_2006/.)

5 Nederlandse Kankerregistratie. (Accessed at www.cijfersoverkanker.nl.)

6 Gospodarowicz MK, Miller D, Groome PA, Greene FL, Logan PA, Sobin LH. *The process for continuous improvement of the TNM classification.* Cancer 2004;100:1-5.

7 Greene FL, Sobin LH. *A worldwide approach to the TNM staging system: collaborative efforts of the AJCC and UICC.* J Surg Oncol 2009;99:269-272.

8 Denoix PF. *TNM Classification.* Bull Inst Nat Hyg 1944:1–69,52–82.

9 Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010.

10 Gonen M, Weiser MR. *Whither TNM?* Semin Oncol 2010;37:27-30.

11 Ben-Porat L, Panageas KS, Hanlon C, et al. *Estimates of stage-specific survival are altered by changes in the 2002 American Joint Committee on Cancer staging system for melanoma.* Cancer 2006;106:163-171.

12 Kattan MW, Karpeh MS, Mazumdar M, Brennan MF. *Postoperative nomogram for disease-specific survival after an Ro resection for gastric carcinoma.* J Clin Oncol 2003;21:3647-3650.

13 Memorial Sloan-Kettering Gastric Cancer Nomogram. (Accessed at www.nomograms.org.)

14 Peeters KC, Kattan MW, Hartgrink HH, et al. *Validation of a nomogram for predicting disease-specific survival after an Ro resection for gastric carcinoma.* Cancer 2005;103:702-707.

15 Novotny AR, Schuhmacher C, Busch R, Kattan MW, Brennan MF, Siewert JR. *Predicting individual survival after gastric cancer resection: validation of a U.S.-derived nomogram at a single high-volume center in Europe.* Ann Surg 2006;243:74-81.

16 Koc M, Dizen H, Ozalp N, Keskek M, Karakose N, Tez M. *External validation of a US-derived nomogram that predicts individual survival after gastric cancer resection.* Langenbecks Arch Surg 2009;394:755-756.

17 Bonenkamp JJ, Songun I, Hermans J, et al. *Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients.* Lancet 1995;345:745-748.

18 Cuschieri A, Fayers P, Fielding J, et al. *Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial.The Surgical Cooperative Group.* Lancet 1996;347:995-999.

19 Hartgrink HH, van de Velde CJ, Putter H, et al. *Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial.* J Clin Oncol 2004;22:2069-2077.

20 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;11:439-449.

21 Degiuli M, Sasako M, Ponti A. *Morbidity and mortality in the Italian Gastric Cancer Study Group randomized clinical trial of D1 versus D2 resection for gastric cancer.* Br J Surg 2010;97:643-649.

22 Okines A, Verheij M, Allum W, Cunningham D, Cervantes A. *Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.* Ann Oncol 2010;21 Suppl 5:v50-54.

23 Ajani JA, Barthel JS, Bekaii-Saab T, et al. *Gastric cancer.* J Natl Compr Canc Netw 2010;8:378-409.

24 Sasako M. *Risk factors for surgical treatment in the Dutch Gastric Cancer Trial.* Br J Surg 1997;84:1567-1571.

25 Hayashi H, Ochiai T, Shimada H, Gunji Y. *Prospective randomized study of open versus laparoscopy-assisted distal gastrectomy with extraperigastric lymph node dissection for early gastric cancer.* Surgical Endoscopy 2005;19:1172-1176.

26 Huscher CGS, Mingoli A, Sgarzini G, et al. *Laparoscopic versus open subtotal gastrectomy for distal gastric cancer - Five-year results of a randomized prospective trial.* Ann Surg 2005;241:232-237.

27 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:S306-311.

28 Lee JH, Han HS. *A prospective randomized study comparing open vs laparoscopy-assisted distal gastrectomy in early gastric cancer: early results.* Surg Endosc 2005;19:168-173.

29 Kim HH, Hyung WJ, Cho GS, et al. *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;251:417-420.

30 Koeda K, Nishizuka S, Wakabayashi G. *Minimally invasive surgery for gastric cancer: the future standard of care.* World J Surg 2011;35:1469-1477.

31 Zhang X, Tanigawa N. *Learning curve of laparoscopic surgery for gastric cancer, a laparoscopic distal gastrectomy-based analysis*. Surg Endosc 2009;23:1259-1264.

32 Luft HS, Bunker JP, Enthoven AC. *Should operations be regionalized? The empirical relation between surgical volume and mortality*. N Engl J Med 1979;301:1364-1369.

33 Birkmeyer JD, Siewers AE, Finlayson EV, et al. *Hospital volume and surgical mortality in the United States*. N Engl J Med 2002;346:1128-1137.

34 Callahan MA, Christos PJ, Gold HT, Mushlin AI, Daly JM. *Influence of Surgical Subspecialty Training on In-Hospital Mortality for Gastrectomy and Colectomy Patients*. Transactions of the Meeting of the American Surgical Association 2003;121:322-332.

35 Finlayson EV, Goodney PP, Birkmeyer JD. *Hospital volume and operative mortality in cancer surgery: a national study*. Arch Surg 2003;138:721-725; discussion 726.

36 Hannan, E. *The influence of hospital and surgeon volume on in-hospital mortality for colectomy, gastrectomy, and lung lobectomy in patients with cancer*. Surgery 2002;131:6-15.

37 Jensen LS, Nielsen H, Mortensen PB, Pilegaard HK, Johnsen SP. *Enforcing centralization for gastric cancer in Denmark*. Eur J Surg Oncol 2010;36:S50-S54.

38 Kuwabara K, Matsuda S, Fushimi K, Ishikawa KB, Horiguchi H, Fujimori K. *Hospital volume and quality of laparoscopic gastrectomy in Japan*. Dig Surg 2009;26:422-429.

39 Learn PA, Bach PB. *A decade of mortality reductions in major oncologic surgery: the impact of centralization and quality improvement*. Med Care 2010;48:1041-1049.

40 Lin HC, Xirasagar S, Lee HC, Chai CY. *Hospital volume and inpatient mortality after cancer-related gastrointestinal resections: the experience of an Asian country*. Ann Surg Oncol 2006;13:1182-1188.

41 Nomura E, Tsukuma H, Ajiki W, Oshima A. *Population-based study of relationship between hospital surgical volume and 5-year survival of stomach cancer patients in Osaka, Japan*. Cancer Sci 2003;94:998-1002.

42 Smith DL, Elting LS, Learn PA, Raut CP, Mansfield PF. *Factors Influencing the Volume-Outcome Relationship in Gastrectomies: A Population-Based Study*. Ann Surg Oncol 2007;14:1846-1852.

43 Xirasagar S, Lien YC, Lin HC, Lee HC, Liu TC, Tsai J. *Procedure volume of gastric cancer resections versus 5-year survival*. Eur J Surg Oncol 2008;34:23-29.

44 Bachmann MO, Alderson D, Edwards D, et al. *Cohort study in South and West England of the influence of specialization on the management and outcome of patients with oesophageal and gastric cancers*. Br J Surg 2002;89:914-922.

45 Birkmeyer JD, Sun Y, Wong SL, Stukel TA. *Hospital volume and late survival after cancer surgery*. Ann Surg 2007;245:777-783.

46 Enzinger PC, Benedetti JK, Meyerhardt JA, et al. *Impact of hospital volume on recurrence and survival after surgery for gastric cancer*. Ann Surg 2007;245:426-434.

47 Ioka A, Tsukuma H, Ajiki W, Oshima A. *Hospital procedure volume and survival of cancer patients in Osaka, Japan: a population-based study with latest cases*. Jpn J Clin Oncol 2007;37:544-553.

48 Thompson AM, Rapson T, Gilbert FJ, Park KGM. *Hospital volume does not influence long-term survival of patients undergoing surgery for oesophageal or gastric cancer*. Br J Surg 2007;94:578-584.

49 Wouters MW, Karim-Kos HE, le Cessie S, et al. *Centralization of esophageal cancer surgery: does it improve clinical outcome?* Ann Surg Oncol 2009;16:1789-1798.

50 Birkmeyer JD, Sun Y, Goldfaden A, Birkmeyer NJO, Stukel TA. *Volume and process of care in high-risk cancer surgery*. Cancer 2006;106:2476-2481.

51 Sonnenday CJ, Birkmeyer JD. *A tale of two provinces: regionalization of pancreatic surgery in Ontario and Quebec*. Ann Surg Oncol 2010;17:2535-2536.

52 The Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland. (Accessed at http://www.augis.org/.)

53 Khuri SF, Daley J, Henderson W, et al. *The Department of Veterans Affairs' NSQIP: the first national, validated, outcome-based, risk-adjusted, and peer-controlled program for the measurement and enhancement of the quality of surgical care. National VA Surgical Quality Improvement Program*. Ann Surg 1998;228:491-507.

54 Hall BL, Hamilton BH, Richards K, Bilimoria KY, Cohen ME, Ko CY. *Does surgical quality improve in the American College of Surgeons National Surgical Quality Improvement Program: an evaluation of all participating hospitals*. Ann Surg 2009;250:363-376.

55 Khuri SF, Henderson WG, Daley J, et al. *Successful implementation of the Department of Veterans Affairs' National Surgical Quality Improvement Program in the private sector: the Patient Safety in Surgery study*. Ann Surg 2008;248:329-336.

56 Tiefenthal M, Nilsson PJ, Johansson R, Glimelius B, Pahlman L. *The effects of short-course preoperative irradiation on local recurrence rate and survival in rectal cancer: a population-based nationwide study*. Dis Colon Rectum 2011;54:672-680.

57 Cunningham D, Allum WH, Stenning SP, et al. *Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer*. N Engl J Med 2006;355:11-20.

58 Macdonald JS, Smalley SR, Benedetti J, et al. *Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction*. N Engl J Med 2001;345:725-730.

59 Biffi R, Fazio N, Luca F, et al. *Surgical outcome after docetaxel-based neoadjuvant chemotherapy in locally-advanced gastric cancer*. World J Gastroenterol 2010;16:868-874.
60 Dikken JL, Jansen EP, Cats A, et al. *Impact of the extent of surgery and postoperative chemoradiotherapy on recurrence patterns in gastric cancer*. J Clin Oncol 2010;28:2430-2436.
61 Dikken JL, van Sandick JW, Swellengrebel HA, et al. *Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS)*. BMC Cancer 2011;11:329.
62 Kim MA, Lee HS, Lee HE, Jeon YK, Yang HK, Kim WH. *EGFR in gastric carcinomas: prognostic significance of protein overexpression and high gene copy number*. Histopathology 2008;52:738-746.
63 Bilous M, Osamura RY, Rüschoff J, et al. *HER-2 amplification is highly homogenous in gastric cancer*. Hum Pathol 2010;41:304-305.
64 Marx AH, Tharun L, Muth J, et al. *HER-2 amplification is highly homogenous in gastric cancer*. Hum Pathol 2009;40:769-777.
65 Sobin LH, Gospodarowicz MK. TNM Classification of Malignant Tumours, seventh edition; 2009.
66 Sasako M, Sakuramoto S, Katai H, et al. *Five-Year Outcomes of a Randomized Phase III Trial Comparing Adjuvant Chemotherapy With S-1 Versus Surgery Alone in Stage II or III Gastric Cancer*. J Clin Oncol 2011;29:4387-4393.
67 Abnet CC, Freedman ND, Hollenbeck AR, Fraumeni JF, Jr., Leitzmann M, Schatzkin A. *A prospective study of BMI and risk of oesophageal and gastric adenocarcinoma*. Eur J Cancer 2008;44:465-471.
68 Lagergren J, Bergstrom R, Lindgren A, Nyren O. *Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma*. N Engl J Med 1999;340:825-831.