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Quality assurance in surgical oncology

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Citation
Peeters, K. C. M. J. (2007, March 28). *Quality assurance in surgical oncology*. Retrieved from https://hdl.handle.net/1887/11462

Version:	Corrected Publisher's Version
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/11462

Note: To cite this publication please use the final published version (if applicable).

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The gastric cancer treatment controversy

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J Clin Oncol. 2003 Jun 15;21(12):2234-6

This editorial was released referring to the following report of Nashimoto et al.

Randomized trial of adjuvant chemotherapy with mitomycin, Fluorouracil, and Cytosine arabinoside followed by oral Fluorouracil in serosa-negative gastric cancer: Japan Clinical Oncology Group 9206-1. J Clin Oncol. 2003 Jun 15;21(12):2282-7

ABSTRACT of the report by Nashimoto et al.

PURPOSE: To evaluate the survival benefit of adjuvant chemotherapy after curative resection in serosa-negative gastric cancer patients (excluding patients who were T1N0), we conducted a multicenter phase III clinical trial in which 13 cancer centers in Japan participated. PATIENTS AND METHODS: From January 1993 to December 1994, 252 patients were enrolled into the study and allocated randomly to adjuvant chemotherapy or surgery alone. The chemotherapy comprised intravenous mitomycin 1.33 mg/m2, fluorouracil (FU) 166.7 mg/m2, and cytarabine 13.3 mg/m2 twice weekly for the first 3 weeks after surgery, and oral FU 134 mg/m2 daily for the next 18 months for a total dose of 67 g/m2. The primary end point was relapse-free survival. Overall survival and the site of recurrence were secondary end points. RESULTS: Ninety-eight percent of patients underwent gastrectomy with D2 or greater lymph node dissection. There were no treatment-related deaths and few serious adverse events. There was no significant difference in relapse-free and overall survival between the arms (5-year relapse-free survival 88.8% chemotherapy v 83.7% surgery alone; P =.14 and 5-year survival 91.2% chemotherapy v 86.1% surgery alone; P =.13, respectively). Nine patients (7.1%) in the chemotherapy arm and 17 patients (13.8%) in the surgery-alone arm had cancer recurrence. CONCLUSION: There was no statistically significant relapse-free or overall survival benefit with this adjuvant chemotherapy for patients with macroscopically serosa-negative gastric cancer after curative resection, and there was no statistical difference between the two arms relating to the types of cancer recurrence. We do not recommend adjuvant chemotherapy with this regimen for this population in clinical practice

Gastric cancer is still a major problem being the most frequent cause of cancer-related deaths, although its incidence steadily declined during the last decades in Western countries. Outside Japan, where a screening program is active, gastric cancer is often diagnosed in an advanced stage. In operable gastric cancer, both the extent of surgery as well as the value of adjuvant treatment remains subject to considerable international controversy. Surgery is the cornerstone in the treatment for gastric cancer. In Japan, a D2 lymph node dissection is the standard surgical procedure, known to have an acceptable safety profile and to result in superior treatment outcome. This extended lymph node dissection was also performed in the randomised trial, reported in this issue of the *Journal of Clinical Oncology* that investigated the role of postoperative adjuvant therapy with Mitomycin C, 5-Fluorouracil and Cytosine arabinoside followed by oral Fluorouracil in serosa negative gastric cancer in combination with surgery versus surgery alone. In fact, 98% of the patients underwent a D2 or greater lymph node dissection. There was one postoperative death in the surgery only arm. Total recurrence rate was almost double in the surgery alone group (13.8 versus 7.1%), indicating a possible role for chemotherapy in the prevention of recurrence. This difference was however not statistically significant. Remarkably was the local control: only 2 patients in the surgery alone arm versus none in the combined treatment arm developed a local recurrence. This excellent local control is probably due to extended surgery. The administered chemotherapy did not lead to a significant difference in relapse free and overall survival when compared to surgery alone. Two hundred fifty-two patients were enrolled in the study and 5-year relapse-free survival was 88.8% in the chemotherapy and 83.7% in the surgery alone arm. The study was designed to detect a 15% difference in 5-year survival. When comparing this percentage for instance with breast cancer, polychemotherapy is administered to early breast cancer patients in the age group over 50 years, based on a meta-analysis of 18,000 patients that showed a 10-year survival benefit of 2 to 3%.(1) To accomplish an increase in 5-year survival rate from 70 to 85% in gastric cancer patients seems rather optimistic, even if they are diagnosed in a relatively early stage (serosa negative, T2). Reaching no significant difference in an underpowered trial is therefore not surprising.

Although a D2 dissection is the generally accepted surgical procedure in Japan, the debate on the benefits of D1 versus D2 lymph node dissection is still ongoing. Convinced of the benefits of a D2 resection, Japanese investigators have always been reluctant to conduct a trial comparing D2 with D1 dissection. In Europe however, two large randomised controlled trials were performed that addressed this issue. The British Medical Research Council Trial(2) could not detect a difference in survival, the 5-year survival rates being 35% for D1 and 33% for D2. Moreover, postoperative morbidity (28% for D1 and 46% for D2) and mortality (6.5% for D1 and 13% for D2) were increased in the D2 arm. Another large-scale randomised trail, set up by the Dutch Gastric Cancer Group(3), proved neither any benefit from D2 lymphadenectomy with regard to survival and local relapse rates. This latter trial included surgical quality control requiring instructing surgeons to be trained in the technique of node dissection by

a Japanese surgeon.(4) Additional quality measures were taken to guarantee the intended difference between D1 and D2 resection. Nevertheless 'contamination' (dissection of lymph nodes outside the indicated area) and 'non-compliance' (incomplete lymph node dissection) were defined and acknowledged as possible confounders of treatment outcome.(5) After excluding postoperative deaths, patients that underwent a curative resection (i.e. R0 resection) had a cumulative risk of relapse of 43% after a D1 dissection and 37% after a D2 dissection (95% confidence interval –2.4% to +14.4%). However, morbidity and mortality were 25% and 4% in the D1 group and 43% and 10% in the D2 group, respectively.(6) Splenectomy was performed in 11% of the D1 patients and in 37% of the D2 patients. Resection of the spleen carried a major risk for hospital death (hazard ratio 2.16) and overall complications (hazard ratio 2.13), while pancreatosplenectomy (30% in the D2 group, 2.6% in the D1 group) increased the risk for surgical complications (hazard ratio 3.34). The operative mortality due to splenectomy in both European trials could have masked a marginal benefit from D2 resection that might have existed. In conclusion however, both randomised trials failed to demonstrate an advantage for the extended D2 procedure. Bozetti et al. clearly showed by multivariate analysis that splenectomy had a deleterious effect on five year survival probability.(7) Deguili et al.(8) showed however in a randomised surgical trial of 153 patients with gastric cancer comparing D1 to D2 dissection that extended lymph node dissection could be performed with low morbidity (9.4% and 16.3% respectively, $p<0.1$) and mortality (1.3% and 0% respectively) in experienced centers. A prospective randomised trial by Wu et al. of 220 eligible patients, comparing D1 with D2/D3 dissection showed equal morbidity (7%) and no mortality in both treatment groups.(9) Taking all these findings into account, a so called 'over D1' lymphadenectomy (i.e. a D1 dissection and retrieval of at least 20 to 25 nodes) might be recommended, based on the finding that the probability of staging a lymph node as tumour positive increases with the number of nodes resected with a plateau reached at 20 to 25 nodes.(10) This recommendation adheres to the principle that lymph nodes are regarded as indicators rather than governors of disease.(11) The controversy between D1 and D2 lymph node dissection seems to be settled by the introduction of the 'over D1' dissection with ommitment of splenectomy and distal pancreatectomy.

The role of (neo-)adjuvant therapy has been debated for a long time as well. Although a meta-analysis(12) of randomised trials to evaluate the effect of adjuvant treatment concluded that postoperative chemotherapy could not be considered as standard adjuvant treatment, both in Japan as well as in Southern Europe many patients routinely receive postoperative chemotherapy. The results of the US Intergroup study by the South West Oncology Group, that indicated a significant overall survival benefit (36 versus 27 months in the surgery alone group) after postoperative chemoradiation, lead to standardisation of this regimen in the United States.(13) During the trial, much attention was paid to quality assurance for radiotherapy, reflected by 35% of the treatment plans that were found to contain major or minor deviations from the protocol and could be corrected before the start of radiotherapy. There

was however criticism on the adequacy of the surgical procedure: although a D2 lymph node dissection was recommended in the protocol, this procedure was only performed in 10% of the cases. 54% of the patients not even had a formal clearance of the N1 tier of regional lymph nodes. This non-compliance clearly undermined survival(14) and led to a high relapse rate of 64% after a median follow-up of 5 years in the surgery only arm compared to 44% after a median follow-up of 6 years in the D1 arm of the Dutch trial. It is clear that the extent and quality of surgery dictates the value of adjuvant treatment. In a considerable part of Europe however, surgery only is the standard of care with increasing emphasis on quality assurance. In Japan, seven early trials, conducted before 1975 used various adjuvant chemotherapy regimes with a comparison to a surgery alone arm. After 1975 the surgery alone arm suddenly disappeared in Japanese multi institutional trials without a definite reason. Therefore 14 trials between 1975 and 1988 were conducted without a surgery alone arm. Four were done to compare different regimes of chemotherapy, two were for dose intensity comparison of a chemotherapy regimen and eight were designed to test the effect of adding an immunotherapeutic agent to the chemotherapy. Mitomycin C (MMC), also investigated in the present study, was almost always used as an inductive agent in combination regiments. Another meta-analysis by Earle and Maroun(15) of 13 trials showed a small but significant survival benefit for patients receiving postoperative chemotherapy. There was an absolute risk reduction from 65% to 61% in relapse-free survival after postoperative chemotherapy, implying 25 patients that are needed to treat to prevent one death. Gastric cancer is a disease in which loco-regional control is difficult to obtain. Gunderson and Sosin showed that relapse in gastric cancer patients after initial 'curative' surgery consisted of local recurrence and/or regional lymph node metastasis in 87.8% of the patients.(16) The high risk of local recurrence prompted some investigators to study the combination of radiotherapy and chemotherapy. In the present study recurrence occurred in 2 patients in the surgery only arm, which means that loco-regional control was very well established by extensive surgery. In the SWOG trial local relapse occurred in 29% and regional relapse in as much as 72% of the patients after surgery alone. Chemoradiaton improved loco-regional control to 19% and 65% respectively, indicating a role for adjuvant treatment in compensating partly for inadequate surgery. However, in the presented Japanese study, the investigated chemotherapy regimen was not capable of further improving treatment outcome. The question remains however whether novel and effective chemotherapeutical agents have a role in combination with optimal surgery to further increase loco-regional control and survival. Large randomised trials with enough power to detect clinically relevant differences are necessary to answer this question. Neoadjuvant treatment seems an attractive option in patients with gastric cancer. It has a potential of down staging enabling curative resection and increased compliance of systemic therapy in patients who often have prolonged morbidity after surgery. Ongoing randomised trials will answer the question whether neoadjuvant chemotherapy has a role in gastric cancer. The MAGIC trial, initiated by the Royal Marsden Hospital and the Institute of Cancer

Research, is investigating the role of pre- and postoperative Epirubicin, Cisplatin and 5-FU (ECF-regimen) chemotherapy in combination with surgery versus surgery alone, and their first results will be anxiously awaited with at the forthcoming ASCO meeting. New treatment regimes based on novel cytotoxic agents like paclitaxel and CPT-11 and biological agents like antiangiogenics and EGFR-mAB might gain a place in the treatment for gastric cancer in the future. The limited role of adjuvant therapy in many trials so far might be due to a residual tumor burden after surgery that is too high, a delayed initiation of chemotherapy, a sample size in trials that is too small, an insufficient acting mechanism of current chemotherapeutics or combination of these. Within Europe, the need for a well-designed prospective randomized trial is acknowledged by the European Organisation for Research and Treatment of Cancer (EORTC) to study the role of effective chemotherapeutic agents (CPT-11, high infusional 5-FU plus leucovorin) in combination with radiotherapy after surgery for resectable gastric cancer. Patients will be treated in specialist centers to ensure optimal surgery which implicates an 'over D1 resection' without splenectomy and preservation of the pancreatic tail, thus minimising postoperative morbidity and mortality. Mandatory will be extensive quality assurance of surgery and radiotherapy and close cooperation with pathology. In this way, the role of adjuvant treatment in combination with optimal surgery will be established. Presently, tools are being developed to identify patients with a high risk of lymph node metastases, which could influence the extent of surgery. Genomic profiling of gastric adenocarcinomas using microarray analysis of chromosomal copy number changes, seems a promising development, enabling a more tailor made treatment.(17) Until then, we can solely rely on the evidence originating from quality-controlled trials. Setting up these kind of trials seems worthwhile to improve treatment outcome in gastric cancer patients.

REFERENCE LIST

1. Polychemotherapy for early breast cancer: an overview of the randomized trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 1998; 352(9132):930-942.
2. Cuschieri A, Weeden S, Fielding J, Bancewicz J, Craven J, Joypaul V et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. Br J Cancer 1999; 79(9-10):1522-1530.
3. Bonenkamp JJ, Hermans J, Sasako M, van de Velde CJ. Extended lymph-node dissection for gastric cancer. Dutch Gastric Cancer Group. N Engl J Med 1999; 340(12):908-914.
4. Sasako M, Maruyama K, Kinoshita T, Bonenkamp JJ, van de Velde CJ, Hermans J. Quality control of surgical technique in a multicenter, prospective, randomized, controlled study on the surgical treatment of gastric cancer. Jpn J Clin Oncol 1992; 22(1):41-48.
5. Bunt TM, Bonenkamp HJ, Hermans J, van de Velde CJ, Arends JW, Fleuren G et al. Factors influencing noncompliance and contamination in a randomized trial of "Western" (r1) versus "Japanese" (r2) type surgery in gastric cancer. Cancer 1994; 73(6):1544-1551.
6. Bonenkamp JJ, Songun I, Hermans J, Sasako M, Welvaart K, Plukker JT et al. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. Lancet 1995; 345(8952):745-748.
7. Bozzetti F, Marubini E, Bonfanti G, Miceli R, Piano C, Gennari L. Subtotal versus total gastrectomy for gastric cancer: five-year survival rates in a multicenter randomized Italian trial. Italian Gastrointestinal Tumor Study Group. Ann Surg 1999; 230(2):170-178.
8. Deguili M, Sasako M, Garino M et al. Outcome of D1 and D2 gastrectomy for gastric cancer. Preliminary results of the Italian Gastric Cancer Study Group (IGCSG) randomized controlled surgical trial. XXXIII World Congress of the International College of Surgeons. October 27-November 1, 2002, Taipei, Taiwan.
9. Wu CW. Preliminary results of gastric cancer surgery trials in a single institute. XXXIII World Congress of the International College of Surgeons. October 27-November 1, 2002, Taipei, Taiwan.
10. Bozzetti F. Principles of surgical radicality in the treatment of gastric cancer. Surg Oncol Clin N Am 2001; 10(4):833-54, ix.
11. Cady B. Lymph node metastases. Indicators, but not governors of survival. Arch Surg 1984; 119(9):1067-1072.
12. Hermans J, Bonenkamp JJ, Boon MC, Bunt AM, Ohyama S, Sasako M et al. Adjuvant therapy after curative resection for gastric cancer: meta-analysis of randomized trials. J Clin Oncol 1993; 11(8):1441-1447.
13. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001; 345(10):725-730.
14. Hundahl SA, Macdonald JS, Benedetti J, Fitzsimmons T. Surgical treatment variation in a prospective, randomized trial of chemoradiotherapy in gastric cancer: the effect of undertreatment. Ann Surg Oncol 2002; 9(3):278-286.
15. Earle CC, Maroun JA. Adjuvant chemotherapy after curative resection for gastric cancer in non-Asian patients: revisiting a meta-analysis of randomised trials. Eur J Cancer 1999; 35(7):1059-1064.
16. Gunderson LL, Sosin H. Adenocarcinoma of the stomach: areas of failure in a re-operation series (second or symptomatic look) clinicopathologic correlation and implications for adjuvant therapy. Int J Radiat Oncol Biol Phys 1982; 8(1):1-11.
17. Weiss MM, Kuipers EJ, Postma C et al. Genomic profiling of gastric cancer predicts lymph node status and survival. Oncogene 2003. In press.