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Quality assurance in surgical oncology

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General introduction and outline of the thesis

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INTRODUCTION

Within medicine there is growing focus on the quality of care delivered. Not only medical professionals strive for increased performance. Also patients, politicians and insurance companies, each having their own and different interest, aim for optimal care. To illustrate the widespread interest for quality, several rank lists have been published in the Dutch laymen's press, qualifying various hospitals to be the "best institution".¹⁻³ Although the quality of medical care is far from easy to define and measure, there is an irreversible tendency of governmental institutions to regulate on the basis of quality. In the Netherlands, the Inspection of Health Care has defined a number of "performance indicators" with the intent to improve quality. According to the Inspection these indicators are all "quantifiable parameters that represent quality, safety, efficacy and accessibility of medical care".⁴ Indicators include, amongst others, hemovigilance for patients undergoing blood transfusion, percentage of unscheduled surgical re-interventions, number of patients with a hip fracture that undergoes surgery within 24 hours, and the fraction of patients diagnosed with breast cancer within five days after presentation. Each hospital is obliged to measure and to disclose its performance on the internet. Consumer pressure is an important factor backing up this system. Although the introduction of performance indicators seems an attractive option, there may be a considerable risk of false interpretation of reported indicators due to methodological and statistical pitfalls.⁵ Moreover, it is argued that performance indicators are determined not only by the quality of treatment, but also by patient characteristics such as age, comorbidity and complexity of disease at presentation.^{6,7} Therefore, it has been suggested that investigating diagnostic and therapeutic processes may gain better insight in the quality of care rather than focussing solely on predefined treatment endpoints.⁸

Despite the fact that the current way of measuring quality may not be optimal, it is an appealing idea that the quality of care is crucial and influences treatment outcome to a considerable extent. However, before any attempt is made to measure quality, it is key to define it first. One could arbitrarily state that the quality of a treatment is determined by comparing it to a standard that is consensus-based and considered as sufficient by medical professionals working in a particular area. For example, experts in the field of rectal cancer treatment have recently stated that MRI is mandatory in the diagnostic work up to assess mesorectal fascia infiltration by the rectal tumour.⁹ In line with this statement, omitting a MRI scan would imply inferior quality of preoperative work up. Another example may be the leaving out of lymph node dissection in the surgical treatment of gastric cancer. Results from a large US randomized clinical trial¹⁰ showed clearly that surgical undertreatment by removing too few lymph nodes is responsible for poor survival.¹¹ Therefore, lymph node dissection should be performed to a certain extent in order to achieve a sufficient quality of surgical care. By reaching consensus in this manner, a definition of acceptable practice emerges that can be referred to when evaluating diagnostic and therapeutic strategies. The development of a standard aids

in reducing variability of treatment outcome between institutions and individual physicians. To develop and maintain a certain standard, a complete set of measures needs to be taken. Only then a predefined level of care can be realised, ranging from accurate and unanimous diagnosis, standardized therapeutic interventions to clear-cut evaluation protocols. All these measures taken together constitute the principle of quality assurance (QA).

Treating solid malignancies has become a matter of team work. Key players are the surgical oncologist, the radiation oncologist and the medical oncologists. Although radiologists and pathologist have become increasingly important in the peri-operative care, their contribution to the quality of oncological care is not discussed in this introducing chapter. QA programmes have been successfully launched by the European Organisation of Research and Treatment of Cancer (EORTC) in the field of both radiation and medical oncology. The EORTC, founded in 1962, with its headquarters in Brussels, Belgium is an organisation that develops, conducts and coordinates laboratory and clinical research throughout Europe in an attempt to improve the management of cancer. The work of the EORTC is funded by the EORTC Foundation, an international association that was established by royal decree under Belgian law. In radiation oncology, as early as 1982, a quality assurance programme was activated in the EORTC Cooperative Group of Radiotherapy.¹² Programmes included dosimetry studies^{13,14} and the development of infrastructure guide-lines in order to implement radiotherapy quality assurance programmes.^{15,16} In medical oncology comparable initiatives were set up: attention has been successfully focussed on local facilities of hospitals with regard to adequate dosing, preparation and administration of cytotoxic drugs.¹⁷ Within the context of quality programmes centers have been visited and facilities for treatment and data management have been reviewed.^{18,19}

Apart from the input by professional organisations, launching new (cytotoxic) drugs is backed up by the pharmaceutical industry, willing to invest considerably in an attempt to have their drugs released. Also, to ensure safety and quality of new drugs, governmental institutions as the US Food and Drug Administration (FDA) and its European counterpart, the European Medicines Agency (EMA) play an important role as well. Despite this governmental interference, withdrawal of promising drugs may become inevitable, as became clear from the withdrawal of rofecoxib (VIOXX), a COX2-inhibitor, showing a rise in cardiovascular events after a secondary safety analysis in comparison to Naprosyn, another non-steroidal inflammatory drug.²⁰ The withdrawal of this money-making drug from the market caused Merck's stock price to fall by 40%, implying a loss of US\$40 billion in market capitalization. The resources that are involved in developing and releasing novel drug are enormous. These financial investments should be counterbalanced against the possible benefits that can be obtained when applying these means in other areas of oncological care.

So what about surgical oncology? Surgery has a major impact on treatment outcome and is the key to cure in patients with solid malignancies. If it's agreed that investing in quality is

worthwhile, the profits of QA programmes are perhaps most pronounced in surgery. However, in contrast to medical and radiation oncology, surgery may seem a less attractive candidate for QA programmes: every operation may be looked upon as a unique event with numerous unpredictable characteristics. Surgery is therapy but not a pill that represents identical timing and dosing in each patient. This possibly leads to the idea that developing a standard of quality of surgical treatment is practically impossible. Meanwhile however, practise has proved the opposite. The advances in rectal cancer surgery illustrate clearly the benefits of surgical QA programmes. From the early days of rectal cancer surgery until recently, local recurrences after rectal cancer treatment have been a major problem. Symptoms of local failure are severe and include rectal blood loss, incontinence and intractable pain.²¹ For many years, aggressive biological tumour behaviour had been held responsible for local failure after rectal cancer surgery. It was Heald who stated for the first time in 1979 that leaving behind mesorectal tissue was responsible for local recurrence rather than the inherent nature of rectal cancer.²² The principle of total mesorectal excision (TME) was born: removing the complete mesorectum with its tumour bearing tissue, resulted in a stunning drop of local recurrences. External audit was considered necessary to validate Heald's results.²³ In the decades thereafter TME has been successfully introduced in many countries: surgeons have been taught in the principles of TME, and local recurrences have dropped and survival has improved concomitantly.²⁴⁻²⁶ Moreover, due to working under vision when enveloping the mesorectum, nerves that are important for sexual and bladder function are now spared and identified, leading to superior functional outcome after pelvic surgery.²⁷⁻²⁹ When comparing the results of TME to those of conventional surgery which involves blunt dissection of the mesorectum, it has to be concluded that there is considerable impact of the type and quality of surgery on clinical outcome parameters such as local control and survival. Keeping this in mind, surgery needs to be standardized and quality-controlled when testing (neo-)adjuvant regimens: only then the role of surgery as a confounding factor can be reduced and the impact of radiation and/or chemotherapy regimens can be assessed reliably. To illustrate this, in the Norwegian Rectal Cancer Project that involved the introduction of TME among surgeons, survival at four years improved substantially from 60% to 73% with a two fold drop in local recurrences.²⁵ For comparison, the 5 year survival rate improvement of 5FU based chemotherapy in stage III colon cancer patients has been "only" 5% from 45% to 50%.³⁰ These figures indicate that the impact of surgery on treatment outcome may be more pronounced than the effect of cytotoxic therapies. Therefore, standardizing and auditing surgery is key in studies investigating experimental (neo-)adjuvant regimes. There are not many studies that control the surgical act. The "TME trial" has been an exception. This prospective randomised trial tested the impact on local control of preoperative short term radiotherapy applying 5x5 Gy in patients with operable rectal cancer who were treated according tot the principles of TME surgery.³¹ A few years earlier the Swedish Rectal Cancer trial had already shown that this radiotherapy regimen was beneficial in rectal cancer patients who were treated with

conventional surgery: both local control as well as survival was superior in irradiated patients (11% vs. 27%, $P < 0.001$ resp. 58% vs. 48%, $P = 0.004$).³² The question that had to be answered was whether radiotherapy was still beneficial in TME treated patients. A pilot phase preceded the TME trial: Y. Moriya from the National Cancer Center Hospital in Tokyo, Japan operated upon 47 Dutch rectal cancer patients obeying the nerve-preserving and TME principles. Local recurrence rate was 7.1%, and it was concluded that nerve preserving did not compromise radicality.³³ In 1996 the TME trial was launched. Running this trial meant introducing the TME technique on a national scale. An extensive QA program was executed in order to standardize surgical treatment and to reduce variation in the quality of surgery between the 84 participating centers.³¹ A unique surgical QA structure was set up: workshops and symposia were organised, an instruction video was distributed and a monitoring committee of experienced instructor-surgeons was installed that gave instructions on-site. In each center, the first five TME operations were supervised by members of the surgical committee. Not only surgery was standardised, but also pathological evaluation of the resected specimens took place according to well defined guidelines as described in the protocol of Quirke et al.³⁴ A panel of supervising pathologists reviewed the results of histopathological examinations. Moreover, the study coordinators of surgery, radiotherapy and pathology checked trial eligibility, treatment and follow-up data. The Central Data Office of the surgical department of the Leiden University Medical Center ensured the quality of all data.³⁵ By executing this structure of extensive data collection and reviewing, a rich database has emerged that encompasses major opportunities for further research. Early results after a median follow-up of two years showed a significant difference on local recurrence rates to the benefit of radiotherapy (2.4% vs. 5.3%, $P < 0.001$) without any difference in overall survival (82.0% vs. 81.8%, $P = 0.84$).³⁶ Introduction of TME in 84 Dutch hospitals applying the surgical QA program seemed successful.

A similar initiative of quality controlled surgical research was already launched in 1989 when the Dutch Gastric "D1D2 trial" was started. This trial investigated the benefits of extended (D2) lymph node dissection in gastric cancer patients. As for rectal cancer, surgery is considered the mainstay of the treatment of gastric cancer. Being worldwide an important cause of cancer mortality³⁷, gastric cancer poses a challenge to oncologists. Not only geographic differences in the incidence of gastric cancer are of interest, also the worldwide discrepancies in treatment outcome furnish food for thought: in Japan where gastric cancer is a common disease, excellent results have been obtained by not only removing the perigastric lymph nodes (the N1 echelon) but also the regional lymph nodes surrounding the great vessels of the celiac axis (N2 echelon, extended (D2) lymph node dissection).^{38,39} Locoregional recurrences are seldomly engaged and survival is outstanding according to Western standards. Moreover, because regional lymph nodes are removed and subjected to pathological examination, gastric cancer patients are better staged as metastases in these nodes will not be overlooked. Convinced of the benefits of extensive lymph node clearance, the Japanese have never been eager to compare it in a prospective randomised fashion to

limited surgery as employed in the West. In an attempt to investigate whether the high quality of the Japanese results could be achieved, the Dutch D1D2 trial was launched.⁴⁰ Patients with histologically proven adenocarcinoma of the stomach without clinical evidence of distant disease, aged under 85 years and fit for surgery were randomised between limited and extended surgery. A sample size of 1062 patients was required to detect a 12% difference in 5 years survival rate between both treatment arms. When comparing two types of surgery in a randomised fashion, formulating and controlling the delivered surgical treatment is of utmost importance. That is exactly what the protocol of D1D2 trial looked after: patients were assigned to one of the two randomisation arms to ensure standardisation of surgery.⁴¹ D1 and D2 dissection were done according to the Guidelines of the Japanese Research Society for the Study of Gastric Cancer.⁴² In these guidelines 16 different lymph node stations are discerned surrounding the stomach. D1 dissection involves removal of the involved part of the stomach together with the lymph nodes along the lesser (stations 1,3 and 5) and greater curvature (2, 4 and 6). D2 dissection implies removal of not only the perigastric (N1) nodes as is done when performing a D1 dissection, but also the regional lymph nodes: along the left gastric (station 7), the common hepatic (station 8), the celiac (station 9) and the splenic arteries (station 10 and 11). Other nodes involve the extraregional stations 12 (hepatoduodenal ligament), 13 (posterior side of the pancreatic head), 14 (the root of the mesentery), 15 (the mesocolon of the transverse colon) and 16 (para-aortic) nodes (see also figure 1, chapter 4). Local surgeons, supervised by the trial coordinator, performed the operations in case of assignment to D1 dissection. One of the 9 referent surgeons performed the D2 dissections. These referent surgeons had been trained in regional nodal dissection by M. Sasako, an experienced Japanese surgeon from the National Cancer Center Hospital in Tokyo, Japan.⁴³ In case of D2 surgery, the surgeon himself divided the specimen into the separate lymph node stations that were further investigated by the local pathologist. Despite this unique programme of surgical QA, protocol violations were engaged, especially in the early phase of trial accrual: non-compliance, i.e. no substantiation of lymphadenectomy by nodal yields of indicated stations, and contamination, i.e. extension of lymphadenectomy outside the allocated level of nodal clearance. These protocol violations reduced the intended distinction between the two types of lymphadenectomy. Therefore, sample size was augmented from the initial 660 patients to 1062. Moreover, the trial coordinators took additional steps to preserve the distinction between limited and extended lymphadenectomy and to improve the accuracy of nodal staging.⁴¹ A few years ago, the final results of this Dutch Gastric Cancer Trial were published: morbidity and mortality were significant higher in the D2 group (25% vs. 43%, $P < 0.001$ resp. 4% vs. 10%, $P = 0.004$). There was no significant difference on overall survival at 11 years of follow-up (30% vs. 35%, $p = 0.53$).⁴⁴ It was concluded that the higher postoperative mortality in case of D2 surgery might have offset the long term survival benefit of extended surgery. As for the TME trial, data collection and verification was a vital part of this study enabling additional analyses on which this thesis is partly based.

Oncological research aims for better treatment outcome, ranging from improved locoregional control and survival to better functional outcome and improved quality life. In addition, the identification of high- and low-risk patients is key in order to deliver (multimodality) therapy with its toxic side effects only to those patient who are most likely to benefit from it. This thesis aims to contribute in meeting this challenge. This thesis was realised with funds from the EORTC. The author was the first EORTC fellow focussing on *surgical* QA aspects of the treatment of cancer. The Dutch Gastric Cancer trial and the TME trial, both incorporating unique surgical QA programmes, constitute the basis of this thesis.

OUTLINE OF THE THESIS

Chapter 2 reviews the advances in gastric and rectal cancer during the recent decades with emphasis on surgical QA programmes. Not only surgery is considered, but also the role of (neo-)adjuvant therapy is discussed.

Chapter 3 is based on a editorial that was released together with the publication of a prospective randomised Japanese trial that investigated the efficacy of postoperative adjuvant therapy with mitomycin C, 5-fluorouracil and cytosine arabinoside followed by oral fluorouracil in serosa negative gastric cancer.⁴⁵ The excellent results of this Japanese trial with only 2 local recurrences out of 252 patients are reviewed, the role of adjuvant chemotherapy is discussed and future directions in optimising gastric cancer treatment are considered.

Chapter 4 deals with the prognostic value “Maruyama Index of Unresected Disease” in gastric cancer patients. As became clear from the British Medical Research Council (MRC) trial⁴⁶ and the D1D2 trial⁴⁰ that both compared prospectively extended (D2) to limited (D1) lymphadenectomy, postoperative morbidity and mortality was substantial in patients assigned to extended surgery. The extent of lymph node dissection was held responsible for this rise in complications. Other risk factors were age as well as organ resection (pancreatectomy and splenectomy were often performed in order not to compromise dissection of stations 10 and 11). At the disclosure of the long-term follow-up data of the D1D2 trial, it was speculated that there might be a benefit of D2 surgery provided that operative mortality is reduced. In an attempt to reduce the risk for postoperative complications, organ preservation is an option, prevention of resecting uninvolved lymph nodes is a possibility too. The latter implies preoperative identification of involved nodes. The Maruyama Computer program sees to this need. The program consists of Japanese database of 3843 gastric cancer patients treated by extensive lymphadenectomy. From all these patients, 7 demographic and pathological patients characteristics that are all known pre-/intraoperatively have been recorded, as well as nodal involvement of the 16 separate lymph node stations as described by the Japanese Research Society for the Study of Gastric Cancer. The program matches cases with similar characteristics and thus predicts the likelihood of nodal involvement. From all

individual patients included in the D1D2 trial, it was recorded which lymph node stations were resected and which were not. Also, the 7 patient characteristics that constitute the basis of the Maruyama Computer program, were known in all curatively operated patients. Based on this information the “Maruyama Index of Unresected Disease” (MI) was calculated: a quantitative measure of residual tumour load in those lymph nodes that were not resected. It was hypothesized that patients with a low MI had superior survival rates. This would imply that using the Maruyama Program can aid in avoiding resection of uninvolved lymph nodes, thus leading to a reduction in postoperative morbidity and mortality without compromising locoregional control and survival. The MI, representing the adequacy and quality of surgical treatment, had already proved to be a strong independent predictor of survival in a large U.S. adjuvant chemo-radiation study.¹⁰ In this U.S. study, the completeness of lymphadenectomy was questioned: as much as 54% of the included patients did not even have clearance of the perigastric (N1) lymph nodes. This surgical undertreatment was held responsible for poor survival and was quantified by the introduction of the concept of MI.¹¹ The prognostic value of MI and its use as guidance for “tailored” lymphadenectomy was investigated in the Dutch D1D2 study population.

One major issue of modern cancer treatment is the individualization of therapy. Rather than relying on general risk groups of patient populations who share similar characteristics, there is growing need for prediction tools that provide individual-based specific information. In this manner patient counselling and adjuvant therapy decision-making may be optimised. For gastric cancer, colleagues at Memorial Sloan-Kettering Cancer Center, New York, U.S., developed a nomogram predicting individual patient risk of tumour-related death after curative resection for gastric cancer.⁴⁷ The nomogram, requiring input from basic patient-related variables, provided a higher predictive ability than the current staging by the International Union Against Cancer. However, the validity of the nomogram was not yet shown in patients from other institutions. **Chapter 5** investigated whether the nomogram was a predictive tool for patients treated in other institutions as well. Four hundred fifty-nine patients from the Dutch Gastric Cancer trial were under investigation: the discrimination ability of the nomogram with respect to 5 and 9-year disease-specific survival was studied and compared to that of the American Joint Committee on Cancer (AJCC) staging system.

As mentioned before, TME for rectal cancer has had significant effects in terms of improved local control and survival. Although these benefits are beyond dispute, there is much concern about the increased risk of symptomatic anastomotic leakage in TME treated patients. The rise in sphincter saving procedures and the subsequent higher proportion of patients with distal bowel anastomoses might contribute to an increase of anastomotic failure. Also, removing the mesorectum may compromise blood supply to the remaining rectum and may thus endanger anastomotic healing. Finally, TME leaves a presacral space for accumulation of haematoma, which can involve into the vulnerable anastomosis leading to a dehiscence. In order to establish an optimal quality of care, all attempt should be made in order to prevent

anastomotic failure. Patients included in TME trial were studied in order to identify risk factors for symptomatic anastomotic leakage in rectal cancer patients who undergo TME surgery. By performing this risk analysis in a large group of patients treated in as much as 84 Dutch hospitals with detailed information on the surgical procedure, guidelines were proposed in order to minimise the risk of anastomotic leakage. The results of this analysis are described in **chapter 6**.

As outlined earlier, the early results of the TME trial has shown that preoperative short term radiotherapy improves local control in rectal cancer patients treated with total mesorectal excision (TME). Moreover, this radiotherapy regimen turned out to be a safe procedure; there was only a slight increase in acute complications when compared with TME alone: Marijnen et al. showed that irradiated patients had 100 ml more blood loss during the operation ($P < .001$) and suffered more often from perineal complications ($P = .008$) in case of abdominoperineal resection.⁴⁸ Apart from “hard endpoints” such as local control and survival, there is a growing awareness that functional outcome and quality of life after combined modality treatment is of interest as well. There are some early reports indicating that radiotherapy, applying two-portal techniques possibly affects urinary bladder and bowel function. In the mean time however, radiotherapy and surgical techniques have been optimised, possibly leading to reduced long term morbidity. To investigate the long term sequela of both TME and radiotherapy, a questionnaire was sent to Dutch patients of the TME trial. **Chapter 7** reports on the results of this study.

Early results of the TME trial at a median follow-up of 2 years revealed significant lower recurrence rates in irradiated patients. Although local failure had always been responsible for poor survival, there was no detectable difference in overall survival between the randomisation arms.³⁶ It was concluded that an effect of radiotherapy was not detected because of the small number of local recurrences and the short follow-up. **Chapter 8** deals with results of the TME trial at a median follow-up of 6 years and investigated whether there was still an effect of radiotherapy on local control and the impact of this effect on survival. In an attempt to tailor radiotherapy to those patients who are most likely to benefit from it, subgroup analyses of the radiotherapy effect in patients with proximal and distal lesions may be of use, as well as for patients with or without nodal involvement. Although subgroup analyses are not to be encouraged from methodological point of view, they may be of use in understanding the biological effect of radiotherapy and in the development of future trials.

In rectal cancer, it is pivotal to perform a radical, curative resection. A positive circumferential resection margin (CRM) is an important predictor for local failure. When free circumferential margins are not likely to be obtained, neoadjuvant multimodality treatments may be valuable with preoperative downsizing as main goal. The Catharina Hospital in Eindhoven is a national referral centre for rectal cancer patients in whom radical resection is deemed unlikely. To assess the efficacy of multimodality neoadjuvant (chemo)radiotherapy in locally advanced rectal cancer, treatment outcome in Eindhoven was benchmarked using a subset

of patients from the TME trial with mobile pT3/pT4 rectal cancer. The results of these analyses are described in **chapter 9**.

In patients with solid malignancies involvement of lymph nodes is an important prognostic factor. Lymph node clearance may serve staging purposes by investigating the removed lymph nodes and thus determining the need for adjuvant treatment. On the other hand, lymphadenectomy may be therapeutic as well by reducing tumour burden and influencing the likelihood of metastatic spread. Lymph node dissection may be associated with postoperative morbidity especially in patients with breast cancer or malignant melanoma. To limit the side effects of lymphadenectomy sentinel node biopsy (SNB) has been introduced: the histopathological state of the sentinel node is presumed to reflect that of all regional lymph nodes. Tumour negative sentinel nodes obviates regional lymphadenectomy. Moreover, sentinel node biopsy offers the opportunity to examine the sentinel node thoroughly applying laborious and focused techniques like immunohistochemistry and reverse transcriptase polymerase chain reaction. In this manner, the presence of so-called minimal residual disease (MRD) can be determined, identifying a subset of patients with a hypothetically worse prognosis. Although this seems a promising strategy, there is a considerable variety in applied SNB techniques and pathological examination which obscures the benefits of SNB and the prognostic value of MRD. **Chapter 10** reviews SNB and MRD in (sentinel) lymph nodes in breast, gastric and colorectal carcinoma, and focuses on the variety of the applied techniques. **Chapter 11** provides a summary of this thesis as well as a discussion on future prospects of improvements of gastric and rectal cancer treatment. **Chapter 12** includes a summary in Dutch.

REFERENCES

1. Algemeen Dagblad. Ziekenhuizen top-100. 19 september 2006
2. Collot d'Escury J, Alma R, Reenen van M, Remmen van T. Steering the right course. Dutch hospitals 2006 - key developments and trends. Amsterdam: Roland Berger Strategy Consultants
3. Leeuwen van A, Wansink W. Gezondheidszorg: de beste ziekenhuizen. Elsevier.2006;62:83-111
4. <http://www.independen.nl/gezondheidszorg/VVZiekenhuizen.aspx>.
5. Kassirer JP. The use and abuse of practice profiles. *N Engl J Med* 1994; 330:634-636.
6. Powell AE, Davies HT, Thomson RG. Using routine comparative data to assess the quality of health care: understanding and avoiding common pitfalls. *Qual Saf Health Care* 2003; 12:122-128.
7. Iezzoni LI. The risks of risk adjustment. *JAMA* 1997; 278:1600-1607.
8. Giard RW. [Performance indicators as a measure of the quality of medical care: rhetoric and reality]. *Ned Tijdschr Geneesk* 2005; 149:2715-2719.
9. Valentini V, Glimelius B, Minsky BD, Van Cutsem E, Bartelink H, Beets-Tan RG, Gerard JP, Kosmidis P, Pahlman L, Picciocchi A, Quirke P, Tepper J, Tonato M, van de Velde CJ, Cellini N, Latini P. The multidisciplinary rectal cancer treatment: main convergences, controversial aspects and investigational areas which support the need for an European Consensus. *Radiother Oncol* 2005; 76:241-250.
10. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, Haller DG, Ajani JA, Gunderson LL, Jessup JM, Martenson JA. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001; 345:725-730.
11. 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; 9:278-286.
12. Horiot JC, van der SE, Johansson KA, Bernier J, Bartelink H. The programme of quality assurance of the EORTC radiotherapy group. A historical overview. *Radiother Oncol* 1993; 29:81-84.
13. Lanson JH, Essers M, Meijer GJ, Minken AW, Uiterwaal GJ, Mijneer BJ. In vivo dosimetry during conformal radiotherapy: requirements for and findings of a routine procedure. *Radiother Oncol* 1999; 52:51-59.
14. Bentzen SM, Bernier J, Davis JB, Horiot JC, Garavaglia G, Chavaudra J, Johansson KA, Bolla M. Clinical impact of dosimetry quality assurance programmes assessed by radiobiological modelling of data from the thermoluminescent dosimetry study of the European Organization for Research and Treatment of Cancer. *Eur J Cancer* 2000; 36:615-620.
15. Kehoe T, Rugg LJ. From technical quality assurance of radiotherapy to a comprehensive quality of service management system. *Radiother Oncol* 1999; 51:281-290.
16. Leer JW, Corver R, Kraus JJ, vd Togt JC, Buruma OJ. A quality assurance system based on ISO standards: experience in a radiotherapy department. *Radiother Oncol* 1995; 35:75-81.
17. Steward WP, Vantongelen K, Verweij J, Thomas D, van Oosterom AT. Chemotherapy administration and data collection in an EORTC collaborative group--can we trust the results? *Eur J Cancer* 1993; 29A:943-947.
18. Vantongelen K, Steward W, Blackledge G, Verweij J, Van Oosterom A. EORTC joint ventures in quality control: treatment-related variables and data acquisition in chemotherapy trials. *Eur J Cancer* 1991; 27:201-207.
19. Verweij J, Nielsen OS, Therasse P, van Oosterom AT. The use of a systemic therapy checklist improves the quality of data acquisition and recording in multicentre trials. A study of the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer* 1997; 33:1045-1049.
20. Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, Lines C, Riddell R, Morton D, Lanis A, Konstam MA, Baron JA. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005; 352:1092-1102.
21. Wiggers T, de Vries MR, Veeze-Kuypers B. Surgery for local recurrence of rectal carcinoma. *Dis Colon Rectum* 1996; 39:323-328.
22. Heald RJ. A new approach to rectal cancer. *Br J Hosp Med* 1979; 22:277-281.
23. MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. *Lancet* 1993; 341:457-460.

24. Kapiteijn E, Putter H, van de Velde CJ. Impact of the introduction and training of total mesorectal excision on recurrence and survival in rectal cancer in The Netherlands. *Br J Surg* 2002; 89:1142-1149.
25. Wibe A, Moller B, Norstein J, Carlsen E, Wiig JN, Heald RJ, Langmark F, Myrvold HE, Soreide O. A national strategic change in treatment policy for rectal cancer--implementation of total mesorectal excision as routine treatment in Norway. A national audit. *Dis Colon Rectum* 2002; 45:857-866.
26. Martling AL, Holm T, Rutqvist LE, Moran BJ, Heald RJ, Cedemark B. Effect of a surgical training programme on outcome of rectal cancer in the County of Stockholm. Stockholm Colorectal Cancer Study Group, Basingstoke Bowel Cancer Research Project. *Lancet* 2000; 356:93-96.
27. Maas CP, Moriya Y, Steup WH, Kiebert GM, Kranenbarg WM, van de Velde CJ. Radical and nerve-preserving surgery for rectal cancer in The Netherlands: a prospective study on morbidity and functional outcome. *Br J Surg* 1998; 85:92-97.
28. Maurer CA, Z'Graggen K, Renzulli P, Schilling MK, Netzer P, Buchler MW. Total mesorectal excision preserves male genital function compared with conventional rectal cancer surgery. *Br J Surg* 2001; 88:1501-1505.
29. Nesbakken A, Nygaard K, Bull-Njaa T, Carlsen E, Eri LM. Bladder and sexual dysfunction after mesorectal excision for rectal cancer. *Br J Surg* 2000; 87:206-210.
30. Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Goodman PJ, Ungerleider JS, Emerson WA, Tormey DC, Glick JH, . Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 1990; 322:352-358.
31. Kapiteijn E, Kranenbarg EK, Steup WH, Taat CW, Rutten HJ, Wiggers T, van Krieken JH, Hermans J, Leer JW, van de Velde CJ. Total mesorectal excision (TME) with or without preoperative radiotherapy in the treatment of primary rectal cancer. Prospective randomised trial with standard operative and histopathological techniques. Dutch ColoRectal Cancer Group. *Eur J Surg* 1999; 165:410-420.
32. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. *N Engl J Med* 1997; 336:980-987.
33. Maas CP, Moriya Y, Steup WH, Klein KE, van de Velde CJ. A prospective study on radical and nerve-preserving surgery for rectal cancer in the Netherlands. *Eur J Surg Oncol* 2000; 26:751-757.
34. Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. *Lancet* 1986; 2:996-999.
35. Kranenbarg EK, van de Velde CJ. Practical information on the conduct of randomized trials. An example from The Netherlands. *Jpn J Clin Oncol* 1999; 29:272-274.
36. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, Rutten HJ, Pahlman L, Glimelius B, van Krieken JH, Leer JW, van de Velde CJ. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001; 345:638-646.
37. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. *Int J Cancer* 1999; 80:827-841.
38. Akoh JA, Macintyre IM. Improving survival in gastric cancer: review of 5-year survival rates in English language publications from 1970. *Br J Surg* 1992; 79:293-299.
39. Soga J, Kobayashi K, Saito J, Fujimaki M, Muto T. The role of lymphadenectomy in curative surgery for gastric cancer. *World J Surg* 1979; 3:701-708.
40. Bonenkamp JJ, Songun I, Hermans J, Sasako M, Welvaart K, Plukker JT, van Elk P, Obertop H, Gouma DJ, Taat CW, . Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. *Lancet* 1995; 345:745-748.
41. Bonenkamp JJ, Hermans J, Sasako M, van de Velde CJ. Quality control of lymph node dissection in the Dutch randomized trial of D1 and D2 lymph node dissection for gastric cancer. *Gastric Cancer* 1998; 1:152-159.
42. Kajitani T. The general rules for the gastric cancer study in surgery and pathology. Part I. Clinical classification. *Jpn J Surg* 1981; 11:127-139.
43. 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; 22:41-48.

44. Hartgrink HH, van de Velde CJ, Putter H, Bonenkamp JJ, Klein KE, Songun I, Welvaart K, van Krieken JH, Meijer S, Plukker JT, van Elk PJ, Obertop H, Gouma DJ, van Lanschot JJ, Taat CW, de Graaf PW, von Meyenfeldt MF, Tilanus H, Sasako M. 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.
45. Nashimoto A, Nakajima T, Furukawa H, Kitamura M, Kinoshita T, Yamamura Y, Sasako M, Kunii Y, Motohashi H, Yamamoto S. 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; 21:2282-2287.
46. Cuschieri A, Fayers P, Fielding J, Craven J, Bancewicz J, Joypaul V, Cook P. 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.
47. Kattan MW, Karpeh MS, Mazumdar M, Brennan MF. Postoperative nomogram for disease-specific survival after an R0 resection for gastric carcinoma. *J Clin Oncol* 2003; 21:3647-3650.
48. Marijnen CA, Kapiteijn E, van de Velde CJ, Martijn H, Steup WH, Wiggers T, Kranenbarg EK, Leer JW. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial. *J Clin Oncol* 2002; 20:817-825.