Quality assurance in surgical oncology

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Koen Peeters

Cover: *David with the Head of Goliath* (1606) by Michelangelo Merisi Caravaggio (1571-1610)

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Kunsthistorisches Museum, Vienna, Austria

David, a shepherd from an early age, developed his courage and fighting skills by defending the flocks from the wild animals that preyed upon them. The free time that being a shepherd provided also allowed him to develop two other skills, that of music and poetry. David was a warrior, and a writer of psalms.

When the Israelites were at war with the Philistines, the two armies faced each other from opposite hills with the Valley of Elah between them. Every morning for forty days, the mighty Philistine Goliath (he may have stood over 9 feet tall) challenged the Israelites for someone to come out and fight him, but none would go out. One day, David, who was actually then too young for the army, arrived with some deliveries for his older brothers. He heard Goliath and immediately volunteered to fight him.

When David explained to King Saul that he had been fighting fierce animals all his life, he convinced the king that he could defeat the Philistine. Perhaps by then the king was willing to try anything to get out of the embarrassing situation, and even if David were not successful the Israelites could always belittle his lack of success with the excuse that David was "just a kid."

After turning down an offer of the king's own armor, which was too big for him, David went down to the creek and got five suitable stones (five, not just one, as any prudent marksman would do when facing a very formidable opponent). He killed Goliath with a single perfectly-accurate shot, perhaps with a little help from an angel – the stone didn't just rebound off the giant man's thick skull as would naturally be expected, but actually penetrated with the power of a modern high-velocity bullet. Upon seeing their hero defeated, the Philistine army made a disorderly retreat, giving the Israelites then in hot pursuit the victory.

Samuel 17:1-58

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Op een dag kwam een weledelzeergeleerd en hoogstbeschaafd heer de Atheense staatsman Themistocles opzoeken met de blijde boodschap dat hij hem de finesses van de toen pas gelanceerde mnemotechniek kon bijbrengen. Themistocles vroeg hem welke boodschap hij dan aan die wetenschap kon hebben. De doctor antwoordde: 'Zij zal u in staat stellen alles te onthouden.' Waarop de staatsman zuchtte: 'Ik wou alleen maar dat u mij kon leren niet te onthouden wat ik maar al te graag zou vergeten.'

De oratore 2, 299
Marcus Tullius Cicero 106-43 v.C.

Aan mijn ouders
Voor Suzan

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1

General introduction and outline of the thesis

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 there 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 intend 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 trial[10] 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 practise 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 (EMEA) 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 mortality[37], 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 mesenterium), 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) trial[46] and the D1D2 trial[40] 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 lympadenectomy. 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.

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2

Quality assurance of surgery in gastric and rectal cancer

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Abstract

Multimodality and quality controlled treatment result in improved treatment outcome in patients with solid tumours. Quality assurance focuses on identifying and reducing variations in treatment strategy. Treatment outcome is subsequently improved through the introduction of programs that reduce treatment variations to an acceptable level and implement standardised treatment. In chemotherapy and radiotherapy, such programmes have been introduced successfully. In surgery however, there has been little attention for quality assurance so far.

Surgery is the mainstay in the treatment of patients with gastric and rectal cancer. In gastric cancer, the extent of surgery is continuously being debated. In Japan, extended lymph node dissection is favoured whereas in the West this type of surgery is not routinely performed with two large European trials concluding that there is no survival benefit from regional lymph node clearance. Postoperative chemoradiation is part of the standard treatment in the United States, although its role in combination with adequate surgery has not been established yet. These global differences in treatment policy clearly relate to the extent and quality of surgical treatment.

As for gastric cancer, surgical treatment of rectal cancer patients determines patient's prognosis to a large extent. With the introduction of total mesorectal excision, local control and survival have improved substantially. Most rectal cancer patients receive adjuvant treatment, either pre- or postoperatively. The efficacy of many adjuvant treatment regimens has been investigated in combination with conventional suboptimal surgery. Traditional indications of adjuvant treatment might have to be re-examined, considering the substantial changes in surgical practise.

Quality assurance programs enable the introduction of standardised and quality controlled surgery. Promising adjuvant regimens should be investigated in combination with optimal surgery.

Keywords: gastric cancer, rectal cancer, surgery, quality assurance

1 INTRODUCTION

In recent years, quality of care is increasingly acknowledged as a crucial factor in the treatment of cancer patients[1]. Keys to improved treatment outcome are multidisciplinary treatment and standardised, quality controlled therapy. These are, at least for a substantial part, integrated into most of the clinical trials. This may partly explain why trial patients often experience a survival advantage over non-participating patients[2]. The goal of (randomised) clinical trials is primarily to prove the advantage of one treatment over the other. Ultimate goal of all research efforts should be however, to improve cancer care for all cancer patients and to expand the knowledge obtained from clinical research to a broader patient population. This means that the level of quality control carried out in a trial, should ideally be maintained in daily clinical practise and integrated into oncological care in a standardised manner. Quality assurance is an area of research that is engaged in evaluating and interpreting variations in treatment and linking them with treatment outcome. To improve outcome, quality assurance focuses on the complete set of systematic actions that is required to achieve a certain standard of care, that is considered possible and feasible to achieve and to maintain. This implies that there is need to formulate a minimum standard of care, to define an acceptable level of variation in treatment outcome, and consequently, to identify factors that are crucial to achieve this standard. Considering the ongoing advances in oncological care, especially in the surgical area, it is key to appreciate these advances for cancer patients and to make every effort to put them into practise.

Although quality assurance is still in childhood, several quality assurance programmes have been employed successfully in chemotherapy[3-6] and radiotherapy[7-14]. In surgery however, that is generally considered the cornerstone of treatment of patients with solid tumours, there has been remarkable little attention for quality control and standardization so far. Of course, surgery is often still looked upon as merely a craft, which may hinder standardization: quantifiable parameters are assumed hard to define and to measure, and each surgical performance is considered a unique event with irreproducible and unpredictable events. However, recent large scale surgical initiatives have undoubtly shown that surgeons are willing to reflect upon their performance and are eager to improve their surgical technique[15-17]. These initiatives showed clearly that training and audit of surgeons is feasible and can result in significant improved local control and survival when compared to historical controls[18]. Through surgical training programmes it has become clear that many treatment failures, that had often been considered to be a result of aggressive biological tumour behaviour, are in fact caused by inadequate local therapy[19]. The changes in surgical practise have to be taken stock of by not only surgeons, but also by radiation and medical oncologists. With the advent of superior surgical techniques, one may have to re-examine the role of (neo-)adjuvant treatment regimens that often have been established in the era of suboptimal surgery. This review deals with the recent developments in the treatment of gastric and rectal

cancer with an emphasis on quality control. Gastric and rectal cancer will be discussed here as surgical treatment of these malignancies is subjected to ongoing debate and has changed substantially in recent decades respectively.

2 GASTRIC CANCER

2.1 Introduction

Although its incidence is declining in Western Europe[20], gastric cancer remains the second most common cause of cancer death worldwide[21]. The decreasing mortality in the West due to gastric cancer is almost solely related to a decreased incidence. This is in contrast to Japan, where apart from the decreasing incidence, overall cure rates are a contributing factor as well. Fuchs and Mayer[22] compared in 1995 stage specific survival between the United States and Japan and noticed remarkable differences in both stage of disease and stage specific 5 year survival rates in favour of Japan. There is some evidence that differences in biological behaviour are responsible for these differences: Japanese patients are younger at the time of diagnosis, have less often proximal lesions, and more often gastric cancer of the "intestinal" type whereas in the West, the diffuse type is more often seen[23]. Bonenkamp et al.[24] compared patient characteristics from Dutch, Japanese en German centers: Japanese patients were on average 3 years younger than German and 8 years younger than Dutch patients, while they had more T4 tumours. Five year survival rates were superior for Japanese patients without an difference in sex distribution, histology and lymph node involvement. In another report from Bollschweiler et al.[25], two patient populations from Germany and Japan were compared. Univariate analysis of 5 year survival rates were 44% and 77% respectively. However, German patients had fewer T1 stage, fewer N0 stage and more M1 stage tumours. Also, they were on average 6 years older and had twice as many proximal tumours. Finally, mass screening as employed in Japan, provides an opportunity to detect gastric cancer in an early stage, and is associated with improved survival rates compared to patients who are not subjected to screening examination[26]. Although the biological differences may at least partly explain the differences in outcome between Japan and the West, the global discussion focuses predominantly on the extent of surgery.

2.2 Surgery

Surgery is the only possible treatment that can lead to cure. On January 22nd 1881, Theodor Billroth was the first to perform a successful operation on a gastric cancer patient, a subtotal gastric resection with a gastro-duodenal anastomosis. The 43 years old woman had a favourable postoperative course, was discharged 26 days after surgery, but died of recurrence 14 months later[27]. For Billroth, the operation was a triumph, and 14 years later, his series comprised 257 cases. Since then, surgical techniques have evolved and improved substantially

with lower rates of postoperative morbidity and mortality and better survival. When looking at a review of articles published in English since 1970, it becomes clear that in recent decades, the number of patients that underwent surgery increased as well as rates of complete resection. These figures are accompanied by mean 5 year survival rates ranging from 21% before the 1970s to 55% in the 1980s[28]. Despite this progress in gastric cancer treatments the global debate on the most appropriate surgical technique is still heated[29].

2.2.1. Extent of gastrectomy

In earlier years, the extent of gastrectomy was still a matter of controversy, especially for cancer in the distal/middle stomach. An *en principle* total gastrectomy, i.e. a total gastrectomy, even when adequate clearance of margins can be obtained by subtotal resection was initially promoted in the United States[30] and France[31] as the preferred surgical treatment. However, several non-randomised series showed that total and subtotal gastrectomy resulted in comparable oncological outcome[32-34]. Moreover, in a Norwegian study, there was a significant lower morbidity rate for subtotal resections in comparison to total gastrectomy(28% versus 38%)[35], which was in line with results from a German study (23% versus 48%)[36]. Also, two convincing prospective randomised trials showed no significant differences 5 year survival rates between subtotal and total gastrectomy[37,38]. The more conservative operation is to be favoured in patients with cancer of the lower or middle stomach, as total gastrectomy is often accompanied by splenectomy which has an adverse effect on postoperative complications and the susceptibility to infections[39-42]. So, one could argue that the extent of gastrectomy is no longer a controversial issue: subtotal gastrectomy is the treatment of choice unless the tumour is localised proximally in the stomach, there is a diffuse tumour growth pattern or a safe proximal margin cannot be obtained. The importance of complete tumour removal was investigated by Songun et al.[43] who showed that margin involvement, which was seen in 5.9% of the evaluable patients in the Dutch Gastric Cancer Trial, was associated with significantly worse survival. It was concluded from this study that frozen section examination should be routinely performed, especially in patients with poorly differentiated, signet ring cell or anaplastic tumours.

2.2.2. Extent of lymph node dissection

Unlike the extent of gastrectomy, the extent of lymph node dissection remains among surgeons subject to heated debate. It was as early as 1889 that Mikulicz propagated lymph node dissection in addition to gastrectomy with removal of the pancreatic tail if necessary[44]. Cunéo showed in 1900 that locoregional lymph nodes played an important role in the metastasis of gastric cancer[45]. Gastric cancer is a disease in which local regional control is difficult to obtain[46]. In order prevent failure and to improve survival, all efforts should be directed toward adequate local therapy. The main discussion centres on the question; what is

adequate local therapy? Is this the territory of the surgeon alone or may have (neo-)adjuvant treatment any value as well?

As mentioned before, reported survival rates have always been consistently better in Japan than in the West. Extended and standardised lymph node dissection as employed in Japan, is according to the Japanese investigators the main explanation for their superior treatment outcome. In the East, it is believed that lymph nodes are *governors* of metastatic disease. According to this philosophy, it is considered crucial to remove these lymph nodes to prevent metastasis and to improve survival. This extended (prophylactic) lymph node dissection is associated with accurate staging, as understaging due to failure to detect tumour involvement of undissected lymph nodes is very unlikely. This approach is contrast to Western believe that states that lymph nodes are merely *indicators* of disease: lymphadenectomy is solely performed in order to stage patients and subsequently to plan adjuvant treatment and not necessary to cure them. Lymph node involvement in gastric cancer is thus thought to be a sign of widespread disease and poor prognosis. These two opposite movements determine the extent of lymph node dissection.

The Japanese Research Society for the Study of Gastric Cancer (JRSGC) has provided strict guidelines for standardization of surgical treatment and pathological examination[47]. According to these guidelines, 16 different lymph node compartments are identified around the stomach (figure 1). Basically, along the lesser curvature stations 1, 3 and 5 are discerned and along the greater curvature stations 2, 4 and 6. these perigastric nodes are grouped N1, whereas nodes along the left gastric (7), common hepatic (8), celiac (9) and splenic (10,11) arteries are grouped N2. Further lymph nodes of stations 13 to 16 have been described. A D1 lymph node dissection entails removal of the greater and lesser omentum and all its perigastric nodes. The extended D2 dissection involves dissecting not only the perigastric nodes, but also the regional N2 nodes. Convinced of the benefits of extended lymph node dissection, Japanese investigators have always been reluctant to perform a randomised trial comparing limited and extended lymph node dissection. In Japan, it is generally considered unethical towards patients and deemed unfeasible among surgeons to run a such trial. Considering the superior outcome in Japan, attempts have been made to introduce extended surgery into the West. Four randomised trials tested D2 against D1 dissection.

Dent et al[48]. were the first to perform a prospective randomised study of gastrectomy with or without D2 dissection. From 1982 to 1986 608 cases were evaluated, and 403 were deemed surgical candidates; as few as 43 patients turned out to be eligible for the trial. The age difference between the two patient populations was remarkable: D2 patients were older (55.8 vs. 45.1 years), and were more often male (15 male patients in the D2 group, 12 in the R1 group). No survival difference was noticed, but the number of patients was very low, which makes it very hard to detect differences that may be small, but clinically relevant to both patients and their doctors. Moreover, there was no explicit quality control and this was a

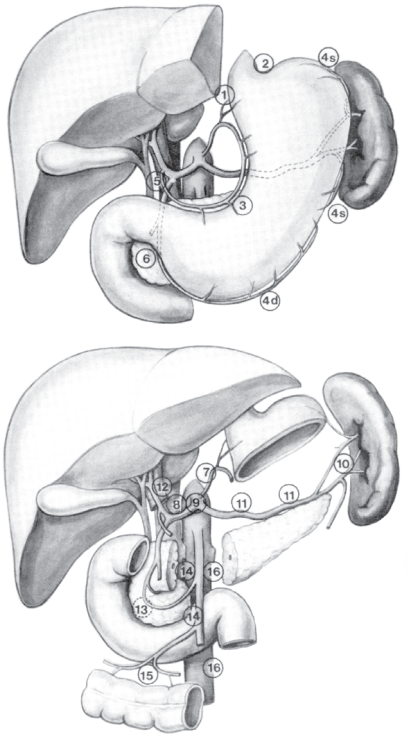

Figure 1. Lymph node stations surrounding the stomach. 1 = right cardial nodes; 2 = left cardial nodes; 3 = nodes along the lesser curvature; 4 = nodes along the greater curvature; 5 = suprapyloric nodes; 6 = infrapyloric nodes; 7 = nodes along the left gastric artery; 8 = nodes along the common hepatic artery; 9 = nodes around the coeliac axis; 10 = nodes at the splenic hilus; 11 = nodes along the splenic artery; 12 = nodes in the hepatodoudenal ligament; 13 = nodes at the posterior aspect of the pancreas head; 14 = nodes at the root of the mesenterium; 15 = nodes in the mesocolon of the tranverse colon.

single institution trial, conducted by only 3 surgeons. Finally, there was a very low eligibility rate, which makes the trial not representative for all patients with gastric cancer.

From 1987 to 1991, 55 patients with antral tumours in Hong Kong underwent subtotal gastrectomy and were randomised to either D1 or D3 dissection[49]. Only 3 surgeons accounted for 75% of the cases. Distal pancreatectomy and splenectomy were part of the D3 dissection. The two patient groups had similar baseline characteristics. Actually, the D1 group had better median survival (1511 vs. 922 days, $p < 0.05$) with a shorter operative time (140 vs. 160 minutes, $p < 0.05$), less blood transfusions ($p < 0.05$), and shorter hospital stay (8 vs. 16 days, $p < 0.05$). One patient died in the D1 group and none in the D3 group (n.s.). Postoperative complications rates (mainly subphrenic abscess and esophagojejunal anastomotic failure) were around 10% and did not differ between the two randomised arms.

From 1986 through 1995 the British Medical research Council set up a prospective randomised trial investigating the possible benefits from D2 dissection over D1 dissection. D1 dissection was defined as a dissection of lymph nodes that were located within 3 centimetres

of the tumour, according to the 1987 TNM classification. D2 dissection concerned dissection of the so called TNM N2 nodes (celiac, hepatodoudenal, retroduodenal, splenic and pancreatic nodes, *depending on the location of the tumour*) with removal of the nodes located at more than 3 centimetres of the tumour. Surgical quality was guaranteed through pre-trial education which consisted of an operative booklet and videotapes of the requested operating procedures. Using a staging laparotomy and intraoperative frozen sectioning, randomisation of ineligible patients (i.e. patients with advanced disease or margin involvement) was limited to only 3 out of 400 randomised cases. The pancreatic tail was removed almost exclusively in the D2 group, the spleen was taken away frequently in both groups, but more often in patients assigned to D2 dissection. With a median follow-up of 6.5 years, 5 year survival rates were 35% for the D1 group and 33% for the D2 group(n.s.)[50]. Splenectomy and resection of the pancreatic tail seriously impacted on survival and proved to be independent predictors of poor survival. Moreover, there was notably increased postoperative morbidity (28% for D1 and 46% for D2) and mortality (6.5% for D1 and 13% for D2) in patients that underwent extended lymph node dissection[51].

Finally, from 1989 to 1993, Dutch gastric cancer patients were randomised between D1 and "Japanese D2 lymphadenectomy". Before the start of the trial, surgeons from 80 centres and eight expert consulting surgeons were extensively instructed to perform surgery according to the protocol of the Japanese Research Society for the Study of Gastric Cancer (JRSGC)[52]. 1078 patients were randomised prior to surgery of whom 82 were excluded for unavailability of a consultant surgeon, poor physical condition or lack of histological confirmation of the diagnosis. Of the remaining 996 patients, 711 underwent the allocated treatment with curative intent. At a median follow-up of 72 months, 5 year survival was 45% for the D1 group and 47% for the D2 group[53]. Morbidity and mortality were 25% and 4% in the D1 group and 43% and 10% in the D2 group respectively[54]. In conclusion, the results of all mentioned randomised trials do not favour the routine use of extended lymph node dissection for gastric cancer, at least not in Western patients.

The matter is however a bit more complicated. The trials that were initiated in South Africa and Hongkong had very few patients randomised and have to be considered underpowered to detect a clinical relevant difference. The British and Dutch trials included a large number of patients and had a good trial design, yet did not detect any significant survival difference. There is however some criticism raised against the two European trials.

First, despite elaborate quality control in the Dutch trial, there were surgical protocol deviations that blurred the intended distinction between D1 and d2 dissection. If lymph node stations were removed that were not to be harvested, this was called "contamination", whereas "noncompliance" was defined as the absence of lymph nodes that had to be harvested according to the protocol. Contamination occurred in 6% of D1 cases and noncompliance in 51% of D2 patients[55]. It became clear that, although detailed treatment guidelines were available, variability among surgeons was considerable. The protocol deviations were detected during

the early phase of the trial, which prompted the investigators to take additional to ensure protocol adherence: expert consultants paid more attention to protocol compliance, lymph node retrieval from the resected specimen was standardised and consistently performed by a specially trained surgical coordinator, immediately after each operation. Notwithstanding these unique efforts, the initiators of the trial concluded themselves that contamination in D1 resections and noncompliance in D2 resections lead to a partial homogenisation of the groups, undermining the likelihood of detecting any potential therapeutic advantage to D2 dissection. The MRC trial did not report on similar problems, simply because they did not investigate the level of surgical non-compliance.

Another important confounding factor in the Dutch and the British trial was the high postoperative mortality caused by splenectomy and pancreatectomy. Both procedures were considered compulsory during the course of the trials to ensure adequate clearance of especially stations 10 and 11. There is ample evidence that pancreaticosplenectomy is associated with increased postoperative morbidity and mortality[56,57], with a significant adverse effect on survival as well[37]. In the Dutch trial, the spleen and pancreatic tail were removed in as many as 38% and 30% of the D2 patients and were responsible for postoperative complications. Preservation of the spleen is important considering the high rates of anastomotic failure in patients that underwent a subtotal D2 gastrectomy. A most likely explanation is that in a D2 dissection, the left gastric artery is divided at its origin, which leads to only a marginal blood supply of the remaining short gastric arteries to the rest of the stomach, thus complicating anastomotic healing. In the meanwhile, organ preservation techniques have become available and are employed successfully with adequate clearance of the regional N2 tier, not only in Japanese but also in Western patients. Dedicated centres in Western Europe have reported mortality rates of less than 5% for extended lympadenectomy with organ preservation[58-60]. In contrary to earlier belief, it has become clear that preservation of the spleen does not compromise survival due to inadequate lymph node removal: a randomised trial from Chile found no survival benefit from splenectomy whereas morbidity was again significantly increased[61]. Another trial in Japan, studying the same matter is on its way[62].

A third and final reason why D2 lymph node dissection did not prove to be superior might relate to the fact that the surgical case load was rather low in both large randomised trials. As many as eighty hospitals participated in the Dutch trial; therefore, a mean of only two patients in any one hospital underwent extended lymph-node dissection in any one year. For this reason, quality control was mandatory, but apparently could not prevent the high postoperative complication rates. Publications on the relation between volume and outcome are numerous, also in gastric cancer, but far from unanimous. A retrospective study by McCulloch[63] and the results of the German Gastric Cancer Study[36] showed clear differences in outcome based on surgical experience whereas no such pattern was discovered among surgeons participating in the Dutch trial[64,65]. Recent reports from experienced centres do suggest however, that outcome improves with higher case-load[66]. This might relate to

low complication rates due to organ preservation that has become part of the standardised D2 dissection in specialized centres. Other factors may include superior surgical skill itself, optimal perioperative care, patient selection bias, or a combination of either these. Fact is however, that surgical gastric cancer treatment is increasingly centralised.

One important issue has been underexposed so far. There is one possible explanation why patients that undergo extended lymph node removal perform better. D2 dissection generally yields more lymph nodes for pathological examination than D1 dissection. The more lymph nodes are examined, the more accurate the staging will be. A so called stage migration[67] may occur when as a result of extended lymph node dissection, a proportion of the patients is assigned to a more advanced stage than would otherwise be the case. Of course, the prognosis is the same in both cases. If this phenomenon takes place, overall results in each stage improve, and the proportion of patients staged as having advanced disease increases. This stage migration has been held responsible for survival differences between Japanese and Western patients. In the Dutch trial, the stage migration effect was estimated by comparing stage specific 5 year survival rates between D1 and D2 patients. Prognosis of TNM stage II patients was 38% for D1 and 43% for D2 patients, for stage IIIA patients these rates were 10% and 29% respectively[68]. Upstaging occurred in as many as 30% of the D2 patients[55]. To limit the blurring effect of stage migration when comparing D1 to D2 dissection, standardization of surgery and pathological examination, as both the surgeon and the pathologist influence the number of lymph nodes that are examined.

So, there is no definite answer as to whether the gastric cancer patient should be treated with extended lymph node dissection or not. Removal of regional lymph nodes that may carry (micro)metastases makes sense either to prevent local failure, and perhaps also to improve survival. In the West, the main drawback from extended surgery has been until recently, the high rates of postoperative complications due to organ removal and/or low case load. The future looks promising with results from experienced centres in the West that have shown low rates of in hospital morbidity and mortality in combination with organ preservation. From quality assurance point of view, interinstitution and intersurgeon variability should be tackled by centralised treatment and strict protocol guidelines with adequate audit to ensure protocol adherence. This includes certainly standardization of pathological examination. There are still some important questions to be answered: is retrieval and investigation of each of the separate 12 or 16 lymph node stations really necessary and feasible in the West? Or is retrieval of at least 15 lymph nodes according to the present TNM classification without any specification on its location sufficient to perform an adequate staging? These questions have to be answered not only for staging purposes, but also to assess the efficacy of adjuvant treatment.

2.3 Adjuvant treatment

Although it is beyond the scope of this review, few words must be said on the role of adjuvant treatment. The discussion centers around the question whether adjuvant therapy is capable of increasing local and distant control and thus improving survival in addition to adequate surgery. This question has remained unresolved so far. The use of chemotherapy in gastric cancer is based on experience in the use of a wide variety of combinations of this modality in therapy for palliative management[69-73]. The chemotherapy regimen FAMTX (high dose methotrexate, high-dose 5 FU, doxorubicine and leucovorin) has been tested in a randomised fashion against 5-FU, doxorubicin and mitomycin (FAM regimen), showing a superior response rate (41% versus 9%, $p < 0.0001$), survival (10.5 months vs. 7.2 months, $p = 0.004$) for patients receiving FAMTX[74]. In concordance with the results of this trial, this regimen was considered a standard therapy in the mid 1990s, at least for patients with advanced disease. A few years later Webb et al.[75] compared FAMT with epirubicin, cisplatin and 5 FU (ECF) in patients with oesofagogastric cancer. ECF proved to be superior with regard to overall response rate (45% vs. 21%, $p = 0.002$) and median survival (8.9 vs. 5.7 months, $p = 0.0009$).

Adjuvant cytotoxic chemotherapy alone has been tested widely during the past three decades, and proven to be of limited value according to an early meta-analysis of Hermans[76]. Recent meta-analyses however, including trials studying novel agents, showed however, a marginal but significant benefit of postoperative chemotherapy[77-79]. The combination of radiation therapy and a fluorinated pyrimidine as a radiation sensitizer may possibly eradicate small amounts of residual or recurrent disease, in both gastric[80] and oesofageal cancer[81]. The US Intergroup study tested whether the combination of 5 FU/LV plus radiation therapy had any value to patients with resected gastric cancer. The study included 556 eligible patients and showed a significant overall survival benefit after postoperative chemoradiation (36 versus 27 months median overall survival in the surgery alone-group, $p = 0.005$). Moreover, there was increased local control after combined treatment with a relapse free survival of 19 months in the surgery alone arm, compared to 30 months in the chemoradiation arm[82]. The results of trial have lead to standardisation of this regimen in the United States. It is remarkable that this decision is based on a study in which 54% of the patients did not have a complete clearance of even the perigastric nodes. Although comparison of patient populations of two separate trials must be made carefully, the differences in outcome with the Dutch trial are striking: 6 year survival rates of Dutch patients undergoing D2 dissection were 47% compared to a 3 year survival percentage of 50% in the superior arm of the US trial. It seems that chemoradiation is capable of at least partly compensating suboptimal surgery. Its role however, in combination with good surgery remains questionable. The American initiators of the trial claim that their patients had more advanced disease than the Dutch patients, which precludes any reliable comparison. Indeed, almost 70% of the US patients had at least a T3 lesion, and 85% had nodal involvement, whereas these figures in the Dutch trial were

27% and 55% respectively. Nevertheless, the level of surgical quality control was remarkable low: patients were randomised after surgery, thus leaving no room for any surgical quality assurance: the only surgical requirements were a "resection with curative intent", and a "en bloc resection". This is in sharp contrast to the level of quality control of the radiotherapy part, reflected by as much as 35% of the radiotherapy plans that were adjusted to avoid toxic effects on critical organs. The marginal attention for the surgical part lead to a shocking 54% of cases that did not even have clearance of the N1 tier. Initiators of the trial showed themselves that the level of surgical undertreatment clearly affected survival[83]. This statement was made using a novel measure of adequacy of lymphadenectomy, termed the "Maruyama Index of Unresected Disease". This index reflects the adequacy of lymphadenectomy in relation to the extent of nodal disease. The basis of the index is a computer program, created by Maruyama and colleagues at the National Cancer Center Hospital in Tokyo, that offers a computerized search of Japanese gastric cancer cases. The program requires a number of individualized demographic and tumour-related input variables, after which similar Japanese cases are collected. The output consists of the percentage likelihood of positive lymph nodes at each of the 16 lymph node stations. The program has proven to provide a valid and accurate prediction of nodal involvement in a large German patient population[84]. The index, as defined by Hundahl et al.[83], represents the sum of predictions of nodal disease for the regional stations that have been left unresected by the surgeon. A high Maruyama Index reflects therefore a high level of residual nodal disease. The index was shown to be an independent predictor of survival in the SWOG trial (median 70, range 0 – 429), which forced the investigators to conclude that surgical undertreatment, as observed in this trial, clearly undermined survival. Presently, the Maruyama Index of Disease is being calculated in the Dutch trial, thus assessing the quality of surgery in this patient population that has less advanced disease compared to the US trial patients.

In conclusion for gastric cancer, substantial progress has been made in the treatment of gastric cancer patients, especially in the surgical area. Adjuvant treatment may have a role either preoperative by increasing resectability and thus local control, or postoperatively by eradicating residual (micro)metastatic disease. To our belief, its efficacy must however be tested in relationship with adequate surgery before it may be considered standard therapy. Surgical and pathological quality assurance is key in future prospective randomised trails that will investigate the role of promising novel chemotherapeutics.

3 RECTAL CANCER

3.1 Surgery

Like for gastric cancer, surgery is the key to cure for patients with rectal cancer. The surgical principles in the treatment of colorectal cancer were formulated for the first time at the

beginning of the twentieth century. Until then local recurrences after surgery for rectal cancer occurred in almost 100% of the cases and postoperative morbidity and mortality were substantial. Miles introduced in 1908 a combined abdominal and perineal approach that was initially associated with high operative mortality (42%)[85]. However, in 1923 Miles reported a large series with postoperative mortality dropping to 10% and local recurrences occurring in 30% of the cases[86]. In the same year Hartmann proposed an alternative technique, a two step procedure for cancers located proximally in the rectum: a colostomy was established at the first operation, after which resection of the tumour took place via the abdomen with the distal part of the rectum left behind at the second operation[87]. Sphincter preserving techniques with restoration of bowel continuity were introduced in recent decades. The obvious advantage of anterior resection is the avoidance of permanent colostomy, which may influence patient's quality of life. The introduction of mechanical stapling devices[88] and the observation that a distal resection margin of 2 centimetres can be considered a oncological safe margin[89,90], led to an increased rate of sphincter saving procedures. The downfall in often mutilating abdominal perineal resections and the accompanying definite colostomies can be considered a major advance in the surgical treatment of rectal cancer patients.

Despite these advances, it still remains difficult to obtain local control after surgical treatment, considering the often high rates of local recurrences that vary considerably between institutions[91-95]. It is important to prevent local recurrences as they cause in disabling symptoms like bleeding, pain and faecal incontinence[96] and often lead to death[97]. The narrow anastomotic boarders of the rectum pose the challenge to the surgeons to remove rectal tumours completely from the pelvic area. In an attempt to improve local control and survival, many surgeons have changed their surgical technique in an essential way. The basic conventional surgical technique involving blunt digital dissection, often resulted in incomplete removal of the mesorectal tissue. Resection of the mesorectum is important as this fatty tissue surrounding the rectum often contains non-nodal foci of metastatic disease that are responsible for local failure[98]. Table 1 shows local recurrence after so called curative surgery in conventional surgery series. Rates from 12% up to 38% have been reported. In addition to this lack of local control, damage to the autonomous pelvic nerve plexus is common leading to sexual [98,99] and bladder dysfunction after surgical treatment [100] .

A major breakthrough was achieved with the introduction of Total Mesorectal Excision by Heald at the North Hampshire Hospital in Basingstoke in 1979[101]. It was postulated that local failure was more a result of leaving behind mesorectal tissue than of the inherent nature of rectal cancer. Meticulous dissection under direct vision to envelope and remove the lymphovascular tissue entirely was hypothesized as crucial to avoid local failure. Few years later Quirke et al.[102] showed that local recurrences were more often seen in patients with involved lateral margins, thus unraveling the major mechanism of local recurrence. In a series of 115 consecutive curative anterior resections by Heald, a cumulative risk of local recurrence at 5 years was as low as 3.7%, with an overall survival rate of 87.5%. No patient received

Table 1. Local recurrence after "curative"conventional surgery; adapted from Kapiteijn et al.[15]

Reference	Patients	Local recurrence (n)	Local recurrence (%)	Remarks
Rao '81[148]	204	44	21.6	
Rich '83[149]	142	43	30.3	
Pahlman '84[150]	197	74	37.6	
Phillips '84[92]	848	124	14.6	
Pilipshen '84[151]	382	105	27.5	27% received preop RT
McDermott '85[152]	934	193	20.7	
Pescatori '87[153]	162	19	11.7	
Athlin '88[154]	99	37	37.4	unknown no. of patients received postop RT/CT
Rinnert-Gongora '89[155]	258	53	20.5	
Zirngibl '90[156]	1153	265	23.0	
Akyol '91[157]	294	49	16.7	
Stipa '91[158]	235	42	17.9	
Adam '94[159]	141	32	22.7	6% received postop RT
Nymann '95[160]	175	37	21.1	
Damhuis '97[161]	902	162	18.0	8% received postop RT
Mollen '97[162]	232	42	18.1	27% received postop RT
Kapiteijn '98[91]	668	150	22.5	36% received postop RT
Kapiteijn '02[18]	269	43	16	

adjuvant therapy. Surprised by these excellent results, independent audit was required to convince colleagues of the validity of the data[103]. In the 1980s, Enker in the United States changed his practise to TME and produced similar results to Heald for local control and survival[104-106]. Aitken documented a series of 64 curatively resected TME cases of which only one had a local recurrence[107]. The acknowledgment of the importance of mesorectal excision led to nationwide programs in Europe to introduce TME. The Norwegian Rectal Cancer Project-initiated in 1993- encouraged and taught surgeons to employ TME surgery[17]. Outcome of total mesorectal excision was compared with conventional surgery. The proportion of patients undergoing total mesorectal excision was 78% in 1994, increasing up to 92% in 1997. The observed local recurrence rate for patients undergoing a curative resection was 6% in the group treated by total mesorectal excision and 12% in the conventional surgery group.

Four-year survival rates were 73% after TME and 60% after conventional surgery. In Sweden a similar project was launched[16]. As part of a surgical quality assurance program, workshops were organized that included 11 television-based demonstrations. Pathology quality control consisted of histopathology sessions in order to teach pathologists to identify possible lateral tumour spread. The study population consisted of all patients who underwent TME surgery in the Stockholm County during 1995 and 1996 (n=447). Outcomes at 2 years were compared with those from the Stockholm I (n=790) and II (n=542) trials as historical controls. Local recurrence occurred in significantly fewer of the TME group than of the Stockholm I and II groups (6% vs. 15% and 14%, $p<0.001$) as did cancer-related death (9% vs. 15% and 16%, $p<0.002$). In the Netherlands, TME was introduced within the framework of the "Dutch TME trial" that investigated the efficacy of preoperative short term radiotherapy in TME treated patients. Patients that underwent curative TME surgery without any adjuvant treatment, were compared with patients from an older trial (cancer recurrence and blood transfusion (CRAB)) in which conventional surgery was performed without any quality control[108]. The local recurrence rate decreased from 16% in the CRAB trial after 2 years to 9% in the TME trial ($p = 0.002$) with a higher overall survival after TME (86% vs. 77%, $p = 0.002$)[18].

TME does not only result in improved oncological outcome. By performing surgery under direct vision of the pelvic area, autonomic nerves that are crucial for bladder and sexual functioning, can be identified and spared. Nesbakken et al.[109] reported a series of 39 TME patients that had a remarkable low frequency of serious bladder and sexual dysfunction. Maurer et al.[110] showed that TME offers a significant advantage with regard to preservation of postoperative sexual function in men. Operative procedures for primary rectal cancer from Japan combine pelvic nerve-preserving techniques with radical tumour resection to ensure optimal local tumour control with minimal bladder and sexual dysfunction. In the Netherlands, a prospective study was undertaken to evaluate functional outcome of TME surgery. Forty-seven patients were operated on by a Japanese surgeon who was familiar with nerve preserving TME surgery. Voiding and sexual function were analysed using questionnaire. Three of 11 women and 19 of 30 men were sexually active. Two men were impotent after operation. Impotence was related to sacrifice of the inferior hypogastric plexus ($p = 0.037$). Preservation of the superior hypogastric plexus was crucial for ejaculation ($p = 0.003$).

So TME results in better local control and survival, increased sphincter preservation[111] and improved functional outcome. However, there is some concern about the increased risk of symptomatic anastomotic dehiscence after TME surgery[107,112,113], which may influence local control in negative way according to a recent publication[114]. The increased rates of anastomotic failure probably relate to the rise in sphincter preservation procedures and the consequent higher proportion of patients with distal bowel anastomoses. Also, TME potentially endangers the blood supply to the remaining rectum, thus jeopardizing anastomotic healing. Finally, removing the mesorectum leaves a large pelvic space for accumulation of an infected haematoma, which bears the risk of sepsis. To avoid severe complications

of anastomotic failure like peritonitis, septic shock and even death, it is crucial to take all possible measures to prevent symptomatic anastomotic dehiscence. The most important measures advocated so far is stoma formation[113,115], especially for the low lying rectal tumours[116,117] Again, there is considerable inter-institution and intersurgeon variation with respect to postoperative morbidity and mortality[118-121]. It is remarkable that there is no unanimous policy among surgeons to minimise the risk for the most important surgical complication after rectal cancer surgery, responsible for significant morbidity and mortality[115,122-125]. In our Dutch TME population, anastomotic leakage occurred in 11.8% of the Dutch patients who underwent an anterior resection (n = 924). A protective stoma formation was done in only 57% of the cases. Patients with a stoma had significant less often a anastomotic leakage than patients that did not have a stoma (16.0 vs. 8.2%, p<0.001). Surprisingly, lack of pelvic drains proved to be the most significant risk factor in the multivariate analysis: 23.8% of patients that did not have pelvic drainage developed a leakage compared to 9.6% of the patients with drainage. Considering the wide variation in rates of postoperative complications and surgical procedures, it is necessary to standardise surgical treatment in order to reduce surgical morbidity of TME.

3.2 Adjuvant treatment

Although not practiced yet worldwide, the impact of total mesorectal excision is beyond dispute. Apart from this significant progress in the surgical area, various adjuvant treatment regimens have shown to improve both local control and survival as well. Radiotherapy, either before or after surgery, has been tested in several major trials[126-133]. The rationale of combining surgery with radiotherapy is that surgery is capable of removing tumour bulk whereas radiotherapy kills peripheral malignant cells in well vascularized tissues surrounding the tumour.

It is being heavily debated whether radiotherapy should be given pre- or postoperatively. Postoperative treatment has the advantage of accurate selection of high risk patients, based on histopathological examination and avoids therefore possible under- and overtreatment in contrast to neoadjuvant treatment. However, the only available randomised trial comparing pre- and postoperative treatment clearly showed the superiority of preoperative radiotherapy regarding side effects and local control (local recurrence rates of 12 and 21% respectively, p = 0.02)[134]. In terms of tumour biology, preoperative radiotherapy is to be preferred to postoperative irradiation as tumour cells before surgery have higher oxygen saturation and are therefore more sensitive to irradiation. Furthermore, preoperative radiotherapy devitalises tumour cells that maybe dispersed during the operation, and reduces therefore the risk of metastasis. In the Swedish Rectal Cancer trial it was shown that a short-term regimen of high-dose preoperative radiotherapy (5x5 Gy) administered in one week was capable of reducing local recurrence rates (27 vs. 11%, p<0.001) and improving 5 year overall survival (48% vs. 58%, p = 0.004) compared to surgery alone. The results are in line with a large meta-analysis,

including 8507 patients from 22 randomised trials that concluded that preoperative is superior to postoperative radiotherapy in terms of cancer specific death (45% and 50% respectively, p=0.0003) and reduction of local recurrence risk (46% and 37%, p=0.002)[135]. Moreover, preoperative treatment has clear advantages in terms of compliance, morbidity and financial costs. Despite these clear benefits, the National Institutes of Health guidelines in the USA still recommends combined postoperative chemoradiation in T3, T4 or N+ patients[136]. To guarantee its effectiveness, postoperative irradiation should start not later than 4 tot 6 weeks after surgery to prevent tumour cell proliferation in the postoperative, fibrous and hypoxic tissues. However, many patients turn out not to be fully recovered from the operation at this point in time, which causes a delay in receiving adjuvant radiotherapy. This lack of compliance jeopardises therefore the possible benefits of postoperative radiotherapy.

Another important indication of preoperative radiotherapy is to achieve downstaging and downsizing in order to facilitate complete resection of locally advanced tumours. The level of downstaging correlates with the fraction size and total dose of radiotherapy applied. To allow enough time to for tumours to reduce in size, the interval between the first day of radiotherapy and surgery needs to be at least 4 weeks. The short term regimen of 5 daily fractions of 5 Gy is not suitable for this purpose, since surgery must be performed as soon as possible after completion of this therapy to avoid surgical complications. So irresectable large tumours should be treated with a conventional radiotherapy scheme of 46 to 60 fractions of 2.0 or 1.8 Gy. After a time interval of 4 to 6 weeks the downsized and downstaged rectal tumours can be resected. It is obvious that complete resection of these tumours without neoadjuvant treatment is not feasible.

Concern has been raised on the toxic effects from adjuvant radiotherapy. In the Stockholm I trial there was 8% mortality in the 5x5 Gy arm compared to 2% in the surgery alone arm[126]. In the Imperial Cancer Research Fund trial these rates were 12% and 7% respectivelty[127]. These unacceptable high proportion of treatment related deaths were clearly due to suboptimal treatment techniques: radiotherapy in these trial was delivered by two opposed fields, which increases the volume treated with the prescribed dose considerably. Results of later trials[134,137], employing adequate treatment techniques, demonstrated that daily 5 Gy fractions can be given safely. In the Dutch TME trial, testing 5x5 Gy in TME treated patients, hardly any acute toxicity from radiotherapy occurred.

Late toxicity of radiotherapy has been described by Frykholm et al.[134] who in showed increased rates of bowel obstruction requiring surgery in irradiated patients. Dahlberg et al.[138] showed that short term preoperative radiotherapy in the Swedish Rectal Cancer trial influenced long-term bowel function, considering the high bowel frequency ($p<0.01$), urgency ($p<0.01$), and emptying difficulties ($p<0.05$) in irradiated patients. Finally, Kollmorgen et al.[139] studied the long term effects of postoperative chemoradiation and concluded that this adjuvant regimen had a major long-term detrimental effect on bowel function. With improved radiation techniques, late toxic effects will be less pronounced. Currently, late

morbidity is being analysed in the Dutch TME trial, using questionnaires to be sent to every patient who is disease-free. The possible late toxic effects have to be counterbalanced against the benefits of radiotherapy on both local control and survival. One of the goals should be to give radiotherapy to those patients only who will benefit the most from it. This of course implies accurate pre-treatment staging.

The benefits of (neo-)adjuvant chemotherapy and/or radiotherapy have all been established in the era of suboptimal conventional surgery. With the advent of TME surgery local control and survival have been improved dramatically. Results from experienced centers have been excellent without the application of any adjuvant therapy at all. So, the question had to be answered whether adjuvant treatment has any value in combination with TME surgery. This issue was addressed by the Dutch Colorectal Cancer Group together with the Nordic Gastrointestinal Tumour Adjuvant Therapy Group and the EORTC that initiated a large prospective randomised multicenter trial to investigate the efficacy of preoperative radiotherapy (5x5 Gy) in combination with TME. Standardization and quality control of surgery, radiotherapy, and pathology were achieved by means of a monitoring committee of specially trained instructor surgeons, a panel of supervising pathologists and study coordinators for surgery, radiotherapy and pathology. Surgical techniques were standardised and the participating surgeons attended workshops and symposiums, saw instructional videotapes and were monitored by specially trained surgeons[140]. Pathologists were taught to identify lateral spread of the tumour according to the protocol of Quirke et al.[102]. A total of 1861 patients were randomly assigned to one of the two treatment groups. Before the start of the TME trial, there were doubts whether the excellent results obtained by specialized surgeons could be matched in a large multicenter trial. There was a low rate of local recurrence after 2 years (8.2%) in the group assigned to surgery alone.[141] This figure indicates that general surgeons, who are adequately trained in the TME surgery, can achieve similar excellent results.

In the Dutch TME trial, preoperatively irradiated patients had an even lower risk of local failure (2.4%) after a median follow-up of 2 years than patients who underwent surgery alone, thus proving that radiotherapy has a value for local control, even when combined with TME surgery. There was no significant difference in survival (82.0% vs. 81.8%, p=0.84). Complete tumour removal proved to be crucial in attempt to prevent local failure. Circumferential margin (CRM) involvement was a strong predictor, independent from TNM classification, for local recurrence: a resection margin of 2 millimetres or less was associated with a local recurrence risk of 16% compared with 6% in patients with more mesorectal tissue surrounding the resected specimen ($p < 0.0001$)[142]. Apart from margin involvement, determination and reportage of the completeness of the mesorectum have proved to be a strong instrument to predict recurrent disease: patients with an incomplete mesorectum had an increased risk for overall recurrence: 36.1% versus 20.3% in the group with a complete mesorectum ($p = 0.02$).[143] This macroscopic direct evaluation of surgery is very informative to the

individual surgeon and can serve as a good tool to audit and subsequently improve surgical performance.

Despite surgical and pathological quality assurance, 18% of the TME treated patients had a positive margin (i.e. 1 millimeter or less), which clearly increased the risk of both local and distant recurrence. So, there is still room for further improvement. Involvement of radiologists may aid in avoiding non-curative resections. MRI provides clear imaging of the surgical plain of dissection and the adjacent tumour deposits. Beets et al.[144] showed that the circumferential resection margin can be predicted with high accuracy and consistency, allowing preoperative identification of patients at risk for unsuccessful tumour clearance. The Pelican Mercury study[145] that compares pretreatment MRI staging with pathological staging in underway and will most likely stress the importance multidisciplinary teams planning multimodality treatment. Establishing a complete resection is crucial as, in the Dutch TME trial, preoperative irradiation had only limited effect in reducing the local recurrence risk in patients with positive margins (9.3% vs. 16.4%, $p = 0.08$). Neither could postoperative radiotherapy prevent local failure in these patients (17.3% vs. 15.7%, $p = 0.98$).[146] In other words, adjuvant radiotherapy can only partly compensate for suboptimal surgery. This underlines once more the importance of "good" surgery.

So based on the results from the Dutch TME trial one may conclude that the problem of local failure has been adequately tackled by both TME surgery and preoperative short term radiotherapy. Survival however, needs to be further improved with an increased proportion of patients dying from distant/liver metastases. Systemic therapy may be of use in an attempt to improve survival, like it is the case in stage III colon cancer. In earlier years, postoperative chemotherapy has been tested in a prospective trial by Taal et al.[147]: there was no significant and disease-free survival benefit from adjuvant 5 FU plus levamisole in rectal cancer patients, possibly due to the fact that there were relatively few rectal cancer patients (n=299), but most likely also due to the 23% of patients with local recurrences, being an important cause of death. One may hypothesize that this high rate of local failure blurred the beneficial effect of chemotherapy on survival. The successor of the Dutch TME-trial, the PROCTOR (Preoperative Radiotherapy and/Or adjuvant Chemotherapy combined with Tme-surgery in Operable Rectal cancer) trial is currently investigating the additional value of postoperative chemotherapy (5-FU/Leucovorin according to Mayo or Nordic regime) in stage II and III rectal cancer patients. The overall survival in the arm treated without chemotherapy is expected to be 60%. Assuming that postoperative chemotherapy leads to an improvement in overall survival from 60 to 70%, 500 patients are needed per arm.

As adjuvant treatment improves with the introduction of superior radiotherapy techniques and novel chemotherapeutic agents, surgical technique has changed dramatically. The data for the superiority of mesorectal excision over conventional surgery are overwhelming. However, adoption of surgical and pathological concepts arising from TME surgery has been remarkably slow so far. Blunt digital dissection is still reported in a 2002 United States surgical

textbook, describing the "sucking noise" when removing the rectum bluntly. When costly and only marginally effective chemotherapy regimens are swiftly introduced into clinical practise, it is astonishing that TME surgery, that has been shown to improve local control, survival, nerve and sphincter preservation dramatically, is not implemented systematically by health care providers. From quality assurance point of view, it is crucial to expand TME surgery beyond the boarders of clinical trials, like it has been done in Norway[17]. Considering its impressive superiority, we believe TME cannot longer withheld from rectal cancer patients. Adjuvant treatment is generally accepted as valuable, but should be tested in combination with TME surgery. Initiators and participants of future trials should embrace the challenge of involving radiologists and pathologists to design new studies with adequate quality control. Only in this way, factors can be identified that may determine patients' prognosis significantly, like inadequate surgery and/or pathological examination. This approach will not only result in improved surgical treatment, but will provide a more reliable assessment of the benefits of adjuvant treatment as well.

4 CONCLUSION

Quality assurance comprises all systematic measures leading to quality controlled diagnosis, pre-treatment staging and multimodality treatment of cancer patients. Large scale surgical quality assurance programs have proven to be feasible and result in significant improved treatment outcome compared to historical controls. Surgery is the main discipline responsible for cure in both gastric and rectal cancer. Therefore, investing in the quality of surgery will yield a substantial profit. This is not only important for cancer patients, but also for all medical professionals who are willing to optimise multidisciplinary treatment and to test new promising treatment regimens in combination with optimal surgery.

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3

The gastric cancer treatment controversy

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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.

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"Low-Maruyama-Index" Surgery For Gastric Cancer A Blinded Re-analysis of the Dutch D1-D2 Trial

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ABSTRACT

A quantitative estimate of residual nodal disease after gastric cancer surgery, the "Maruyama Index of Unresected Disease" (MI), proved a strong independent predictor of survival in a large U.S. adjuvant chemo-radiation study in which surgical under-treatment was frequent. Data from the Dutch D1-D2 Lymphadenectomy Trial permits an opportunity to assess the prognostic value of this variable in a cohort with lower-stage disease treated with minimum D-1 lymphadenectomy and no adjuvant chemoradiation. Methods: Blinded to survival, and excluding those cases with missing information, MI could be calculated for 648 of the original 711 patients treated with curative intent. Survival was assessed by log rank and multivariate Cox regression analysis. All cases have been followed for a minimum of 11 years. Results: Overall Dutch Trial findings were not impacted by the absence of 63 cases with incomplete data. As expected, median MI was 26, much lower than in the previous U.S. study. In contrast to D level, MI < 5 proved a strong predictor of survival by both univariate and multivariate analysis. MI was an *independent* predictor of both overall survival (p= 0.016, HR=1.45, 95% CI 1.07-1.95) and relapse risk (p= 0.010, HR=1.72, 95% CI 1.14-2.60). Strong "dose-response" with respect to MI and survival was also observed. Conclusions: We conclude that in this trial, "low-Maruyama-index" surgery is associated with enhanced survival, whereas, outside of certain sub-groups, routine D-2 lymphadenectomy is not. This observation suggests that surgeons might better impact on patient survival by achieving a "low-Maruyama-index" operation rather than a particular d-level.

INTRODUCTION

Intergroup 0116 (SWOG 9008) , a two-armed prospective, randomized multi-center North American trial, established the value of postoperative, 5-FU-based, adjuvant chemo-radiotherapy for gastric cancer patients with sufficient caloric intake, good performance status, and adequate organ function.[1] While this conclusion has been questioned for certain subgroups, such as UICC Stage I-B cases, [2] and, more recently, cases with diffuse histology,[3] such adjuvant chemo-radiotherapy is now considered standard in North America.

Data elements capturing the extent of surgery and the extent of lymphadenectomy for Intergroup 0116 patients were meticulously collected and analyzed prior to any survival analysis. Although printed trial materials recommended D2 lymphadenectomy and included appropriate instructions, the extent of surgery was not mandated beyond the requirement that all margins of resection be negative and there be no identifiable residual disease. The nature of postoperative registration largely thwarted effective communication of such surgical recommendations, and the trial captured existing patterns of surgical care in North America during the accrual period, 8/'91 - 7/'98. Disappointingly, 54% of cases had less-than-D-1 lymphadenectomy ("D-0 lympghadenectomy"), and only 10% underwent D-2-or-greater lymphadenectomy.[1, 4] Critics of the trial emphasize it might have been positive because of high average burden of unresected regional nodal disease.[2]

Anticipating this possibility while the trial was still accruing, and funding a separate study to assess potential survival impact, one of the authors (S.H.) attempted to quantify the likelihood of unresected nodal disease for each INT 0116 patient by defining a so-called "Maruayama Index of Unresected Disease" or "Maruyama Index" (MI).[4] To calculate MI, the "Maruyama Computer Program" [5] was used to estimate the percentage likelihood of nodal involvement for each "regional" lymph node station left in situ by a given patient's surgeon. For the purpose of this analysis, "regional" was defined as in JRSGC [6] node stations #1 through #12 (see Figure 1). For the benefit of those unfamiliar with this tool, the "Maruyama Computer

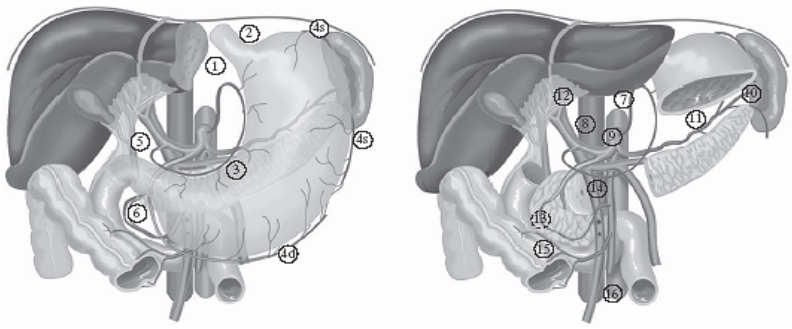

Figure 1. Defined lymph node stations. Stations #1-#16 are defined by the Maruyama Program. Stations #1-#12 are deemed "regional" and used for "Maruyama Index of Unresected Disease" (MI) calculations.

Program" [5] simply matches a given case with very similar cases previously treated at the National Cancer Center Hospital in Tokyo. The large number of cases in the N.C.C. Tokyo data base (3,843 cases, and recently expanded [7]) serves to make the nodal predictions of this computer program very accurate, not only for Japanese cases, but for cases from Germany and Italy as well.[5, 8, 9]. The "Maruyama Index of Unresected Disease" or "Maruyama Index" (MI) is defined as simply the sum of regional nodal disease percentages for "regional" node stations (#1-#12) not removed by the surgeon. Prior to any survival analysis, it was predicted that those with MI<5 would enjoy higher survival.

Despite differences in median survival (i.e. 27 months for D-0, 29 months for D-1, and 48 months for D-2), d-level failed to prove a significant predictor of survival in Intergroup 0116. However, in contrast to d-level, "Maruyama Index of Unresected Disease" (MI) proved, on both

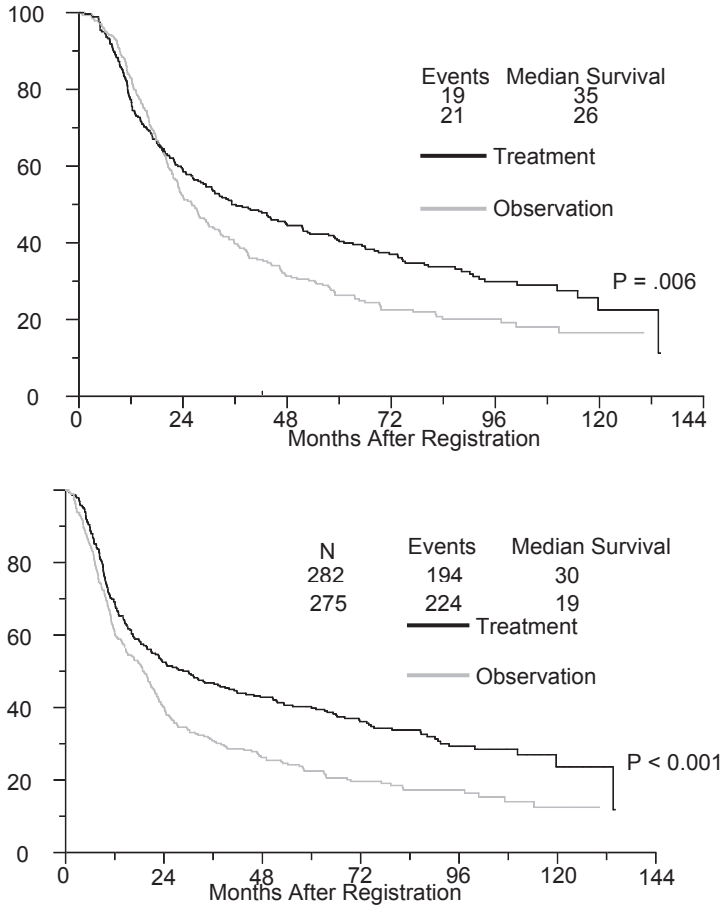

Figure 2. Updated overall survival curves for Intergroup 0116 chemoradiation cases. Overall survival (a) and relapse-free survival (b). Data kindly provided by the Southwest Oncology Group (see references 4 and 10)

univariate analysis (see updated survival curves in Figure 2a and 2b) and multivariate analysis to be a significant predictor, with a dose-response effect also noted. For cases with MI < 5 vs. MI ≥ 5, median overall survival was 87 months vs. 27 months (p=0.005). Median relapse free survival was 87 vs. 20 months (p=0.001). With T, N, and treatment group as covariates, hazard ratio was 1.9 for overall survival (95% CI 1.3-2.8) and was 2.0 for disease-free survival (95% CI 1.4-2.9).[4, 10]

Each case in the Dutch D1-D2 Trial has now been followed for a minimum of 11 years. Outside certain subgroups, (e.g. the subgroup with N-2 disease) the trial remains negative overall.[11] Compared to cases in the Intergroup Trial, cases in the Dutch Trial had generally lower-stage disease and also received more adequate surgical treatment. For example, 69% of Dutch cases were node-negative, versus only 15% in the Intergroup cases. Additionally, all but 137 (non-compliant) cases of the 711 treated for cure in the Dutch Trial received at least a D1 lymphadenectomy. Finally, none of the cases received adjuvant postoperative therapy. These facts, combined with the detailed lymphadenectomy data collected for each Dutch D1-D2 Trial participant, made Maruyama Index analysis attractive. We now report a blinded post hoc analysis of the impact of MI on survival and recurrence in this trial.

METHODS

Entry criteria, informed consent, randomization, surgical treatment, and quality control for the Dutch D1-D2 trial have been reported previously.[12, 13]

In the late 80's, Dr. K. Maruyama and colleagues at the National Cancer Center Hospital in Tokyo created a computer program (known as the "Maruyama Program") which searched their meticulously-maintained 3,843-patient database of gastric cancer cases treated by extensive lymphadenectomy, matching cases with similar characteristics to a given case. With seven demographic and clinical inputs (all identifiable pre-operatively or intra-operatively), the program predicts the statistical likelihood of nodal disease for 16 (JRSGC-defined [6]) nodal stations around the stomach (see Figure 1). Maruyama Program predictions have been assessed in Japan, Germany, and Italy, and found to be highly accurate.[5,8,9] The original version of the Maruyama Program was used for the Intergroup-0116 analysis. A CD-ROM with expanded case volume has recently been released,[7] and this was used for all but 19 of the MI calculations in the current study.

As noted in the introduction, the *"Maruyama Index of Unresected Disease" (MI)* has been defined (by author SH) as *the sum of Maruyama Program predictions for those regional node stations (stations #1-#12) left in situ by the surgeon.*[4] An identical definition was used for this study.

Data sufficient for MI calculation was available for 648 of the original 711 cases resected for cure in the Dutch D1-D2 Trial, and these constitute the basis for this study.

Table 1. Surgical and pathological characteristics by D-level of 648 Dutch Trial cases after excluding those cases with missing information for the calculation of "Maruyama Index of Unresected Disease" (MI). Distribution by D-level of lymphadenectomy. Percentages in parentheses. Statistics: Pearson Chi-square.

	D1	D2	P-value
Site of tumor			
Proximal	32 (50.8)	31 (49.2)	
Middle	96 (53.9)	82 (46.1)	0.967
Distal	181 (52.8)	162 (47.2)	
Diffuse	35 (54.7)	29 (45.3)	
Type of gastrectomy			
Distal/subtotal	237 (55.8)	188 (44.2)	0.059
Total	107 (48.0)	116 (52.0)	
T stage			
T1	91 (54.2)	77 (45.8)	
T2	164 (53.4)	143 (46.6)	0.272
T3	86 (53.4)	75 (46.6)	
T4	3 (25.0)	9 (75.0)	
N stratum (UICC 1997)			
N0	150 (54.2)	127 (45.8)	
N1 (1-6 nodes positive)	123 (53.0)	109 (47.0)	0.101
N2 (7-15 nodes positive)	47 (54.0)	40 (46.0)	
N3 (≥16 nodes positive)	14 (35.9)	25 (64.1)	
M1	10 (76.9)	3 (23.1)	
UICC stage			
IA	69 (53.1)	61 (46.9)	
IB	84 (55.6)	67 (44.4)	
II	88 (54.3)	74 (45.7)	0.428
IIIA	54 (51.9)	50 (48.1)	
IIIB	24 (60.0)	16 (40.0)	
IV	25 (41.0)	36 (59.0)	

Paralleling the previous Intergroup analysis, an MI cutoff of 5 was used for the initial univariate survival analysis.

For statistical analysis the SPSS programme was used. A p-value of 0.05 was considered statistically significant. Overall survival was calculated from the day of randomisation until either day of death (event) or day of last follow-up (censored). Relapse was also calculated from the day of randomisation. Data for a patient was censored when at last follow-up contact the patient was alive with no evidence of disease or had died of non-neoplastic cause without evidence of recurrence. Distribution by D-level was assessed by Pearson Chi-square. Distribution by MI was assessed by the non-parametric Kruskal-Wallis test. Survival and relapse risk was assessed by log rank and multivariate Cox regression analysis.

All cases were followed for 11 years or more.

RESULTS

Median age of the 648 cases was 66 years. Fifty-six percent were male. Distribution according to D-level by tumor site, T-stage, nodal stratum, type of gastrectomy, and UICC stage largely paralleled that of the originally reported 711 patients (Table I).[12]

As shown in Table 2, overall median MI for the 648 cases was 26. Median MI generally increased with advancing UICC stage, number of nodes positive, T-stage, D-level, and tumor involvement of overlapping sites, in that order. Tumors involving overlapping gastric sub-

Table 2. Maruyama Indices according to surgical and pathological characteristics. Percentages in parentheses. Statistics: Non-parametric testing according to Kruskal-Wallis

Variable	N	Median MI	Range	Interquartile range	P-value
Overall	648	26	0 – 350	5 – 70	
Site of tumor					
Proximal	63 (9.7)	20	0 – 220	6 – 50	
Middle	178 (27.5)	23	0 – 350	4 – 74	0.026
Distal	343 (52.9)	24	0 – 228	5 – 64	
Diffuse	64 (9.9)	63	0 – 286	19 – 131	
Type of resection					
Distal/subtotal	425 (65.6)	21	0 – 228	4 – 64	0.060
Total	223 (34.4)	33	0 – 650	8 – 80	
Randomisation					
D1	344 (53.1)	50	0 – 350	12 – 100	<0.001
D2	304 (46.9)	10	0 – 228	0 – 35	
T stage					
T1	168 (25.9)	2	0 – 54	0 – 9	
T2	307 (47.4)	35	0 – 220	10 – 63	<0.001
T3	161 (24.8)	86	0 – 350	37 – 141	
T4	12 (1.9)	67	0 – 228	25 – 129	
Number of positive nodes					
N0	277 (42.7)	11	0 – 220	1 – 50	
N1 (1-6 nodes positive)	232 (35.8)	35	0 – 350	6 – 74	<0.001
N2 (7-15 nodes positive)	87 (13.4)	40	0 – 243	19 – 105	
N3 (≥16 nodes positive)	39 (6.0)	42	0 – 280	16 – 76	
M1	13 (6.0)	92	3 – 217	17 – 134	
UICC stage					
IA	130 (20.1)	2	0 – 54	0 – 8	
IB	151 (23.3)	24	0 – 199	8 – 62	
II	162 (25.0)	37	0 – 220	10 – 75	<0.001
IIIA	104 (16.0)	61	0 – 350	25 – 102	
IIIB	40 (6.2)	107	7 – 243	27 – 157	
IV	61 (9.4)	50	0 – 280	17 – 87	

sites (i.e. "diffuse" site) had a median MI of 63, significantly higher than for more localized tumors (P=0.03). Median MI was also higher for D1 cases (MI= 50 vs. 10, P=0.01).

Unsurprisingly, D1 and D2 survival curves for the 648 case cohort are similar (Figure 3).

Only 154 cases had MI < 5. Overall survival (Figure 4) appears higher and relapse risk lower (not shown) for these cases (p<0.001 by log rank test for both comparisons).

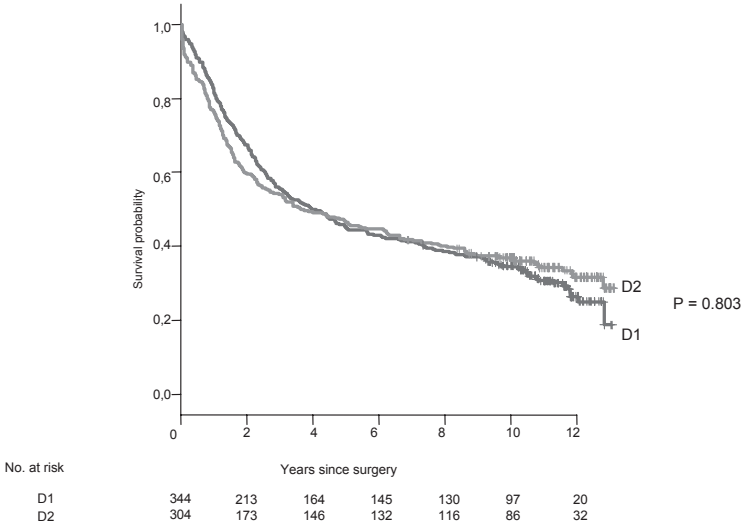

Figure 3. Overall survival for 648 cases according to D-level randomization

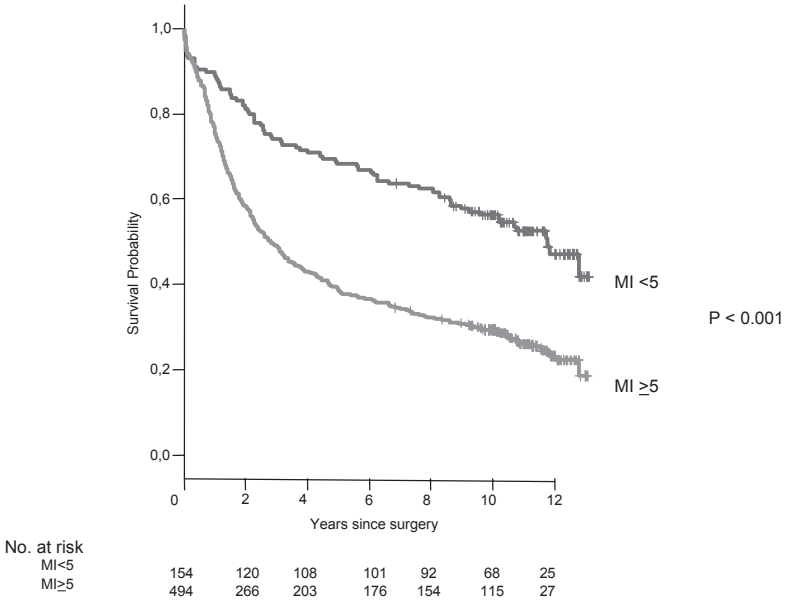

Figure 4. Overall survival for 648 Dutch Trial cases, according to MI <5 vs. MI >=5 status

Table 3. Multivariate Cox regression analysis of overall survival for 648 cases

Variable	Hazard ratio	95% CI	P-value
MI (<5 vs ≥5)	1.45	1.07 – 1.95	0.016
T stage			<0.001
T1	1.00		
T2	1.23	0.91 – 1.67	0.171
T3	1.87	1.33 – 2.65	<0.001
T4	2.22	1.15 – 4.29	0.018
N stratum (UICC 1997)			<0.001
N0	1.00		
N1	1.96	1.55 – 2.48	<0.001
N2	2.74	2.02 – 3.71	<0.001
N3	4.53	3.03 – 6.76	<0.001
M1	3.86	2.00 – 7.43	<0.001
Randomisation			
D1	1.00		
D2	0.95	0.77 – 1.16	0.610
Residual tumour			
R0	1.00		
R1	2.14	1.54 – 2.97	<0.001
Age	1.04	1.04 – 1.03	<0.001

Mutivariate Cox regression analysis reveals hazard ratios for overall survival as depicted in Table 3 and for disease-free period as depicted in Table 4. In contrast to D-level, MI was a significant independent predictor of overall survival and disease-free interval.

Overall survival (Figure 5) and relapse risk (not shown) by MI quartiles indicate what may be termed a "dose-response" effect with respect to likelihood of residual nodal disease as estimated by MI. Survival is highest for the low MI quartile and poorest for the high-MI quartile.

DISCUSSION

Median MI for the 648 cases in this study is 26. For cases in the previous Intergroup Trial, it was 70. This is not surprising given the 54% D0 rate in the latter study.[1, 4]

Nodal staging in this study is more accurate than for Intergroup Trial cases. More nodes were resected and pathological assessment of these nodes was more detailed.[12, 13]

The relationship between MI, T-stage, nodal stratum, and UICC stage is complicated. If one hypothetically holds the extent of lymphadenectomy constant, higher-stage, more advanced tumors will tend to have a higher likelihood of disease in un-dissected regional node stations and, therefore, a higher MI. Such linkage with T-stage and nodes positive potentially biases the analysis against significance for MI in a multivariate analysis. Nevertheless, in multivariate

Table 4. Multivariate Cox regression analysis of disease free period for 648 cases

Variable	Hazard ratio	95% CI	P-value
MI (<5 vs ≥5)	1.72	1.14 – 2.60	0.010
T stage			<0.001
T1	1.00		
T2	2.06	1.28 – 3.21	0.003
T3	3.24	1.95 – 5.40	<0.001
T4	4.25	1.90 – 9.51	<0.001
N stratum (UICC 1997)			<0.001
N0	1.00		
N1	3.98	2.82 – 5.62	<0.001
N2	5.39	3.60 – 8.08	<0.001
N3	9.10	5.56 – 14.89	<0.001
M1	6.69	3.18 – 14.06	<0.001
Randomisation			
D1	1.00		
D2	1.15	0.89 – 1.48	0.279
Residual tumor			
R0	1.00		
R1	2.44	1.72 – 3.47	<0.001
Age	1.01	1.00 – 1.02	0.041

Cox regression analysis, correcting for T and N, MI remains a strong independent predictor of survival and relapse-free survival. When MI is divided in quartiles, as depicted in Figures 5, there is clear and significant "dose-response" with respect to survival and relapse risk. This further supports the prognostic value of MI.

D-level derives from the detailed and somewhat complicated Japanese Research Society for Gastric Cancer (JRSGC) definitions of nodal levels.[6] This scheme assigns, based on tumor location, a nodal level (N-1 through N-4) for each defined nodal station around the stomach, upper abdomen, and pera-aortic areas. In a D1 lymphadenectomy, all N-1 level node stations are removed, but not all N-2 level node stations. In a D2 dissection, all N-1 and N-2 nodal stations are removed, but not all N-3 nodal stations. D3 and D4 dissections are similarly defined. In general, all JRSGC N1 and most N2 nodal stations are considered "regional" by North American surgeons, and N3 and N4 nodes are generally considered "extra-regional." MI is calculated according to: a) the status (dissected or undissected) of "regional" node stations #1-#12; b) the Maruyama Program prediction of disease in any of the nodes of that station (i.e. percent likelihood of disease); and c) whether or not the surgeon has dissected the station. Worldwide, because gastric cancer is now staged according to UICC/AJCC TNM definitions, surgeons - particularly Western surgeons - not thoroughly familiar with the complicated JRSGC system have difficulty precisely defining which node stations need to be dissected for a "D1" or "D2" lymphadenectomy. In contrast, running the Maruyama Program either pre-

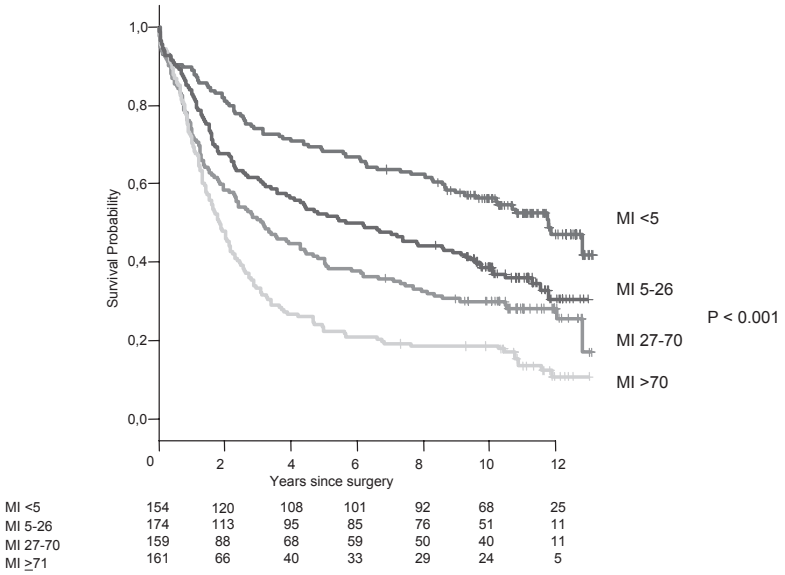

Figure 5. Overall survival for 648 Dutch Trial cases, by MI quartile. A "dose response" for estimated unresected disease, as quantified by MI, is evident

operatively or intra-operatively, and seeing visual and tabular output for quantified risk of disease in all defined regional nodal stations[7] is probably easier in the era when laptop computers and PC computers are available in most operating room suites.

Moveover, three separate prospective, randomized trials of D-1 versus D-2 lymphadenectomy have failed to show consistent value for routine use of more-extensive D2 lymphadenectomy.[12, 14, 15] Three additional trials of routine total gastrectomy, with or without extensive lymphadenectomy, have failed to show improved survival.[16-18] Scant data concerning results with D-0 lymphadenectomy are available because most experts consider this inadequate surgical treatment.

Despite the enormous expertise and experience involved in their derivation, the JRSGC definitions for N-level and D-level are arbitrary. In contrast, Maruyama Program output reflects actual experience with actual tumors of precisely matched characteristics, drawn from a staggeringly large data base. As noted, previous work has shown Maruyama Program predictions to be quite accurate.[5, 8, 9]. Surgeons adhering to the time-honored concept of trying to match the extent of surgical resection with the extent of regional disease should find the Maruyama Program a useful tool. In any case, the arbitrary and complicated, "D-level," JRSGC approach has not proven helpful.[11, 12, 14-18]

Both the MRC and Dutch Trials document that in European patients, JRSGC-defined D2 dissections (i.e. more extensive - but arbitrarily-defined – node dissections) are associated with significantly higher 30-day and in-hospital postoperative mortality (13% vs. 6.5% for the MRC Trial and 10% vs. 4% for the Dutch Trial), with much of (but not all of) the excess

mortality deriving from associated pancreatic-splenic resection in the D2 groups.[12, 15, 19, 20] Pancreas/spleen-preserving lymph node dissections are now advocated. Particularly since gastric cancer patients tend to be older, with frequent co-morbid conditions, limiting lymphadenectomy to only nodal stations at risk may decrease postoperative mortality by decreasing tissue trauma and decreasing operative time. The Maruyama Program represents a tool to facilitate this.

Only 154 cases had MI < 5, despite the protocol mandate that half the cases be treated with D2 dissection. Median MI for the D2 cases was 10. Fifty-one percent of the D2 cases in the trial had less-than-D2 dissection because of pathology-determined non-compliance with the protocol (i.e. no nodes found in 2 or more node stations which should have been dissected). [11, 12, 21] This may explain why so few of the cases had MI < 5. It must also be emphasized, however, that some "compliant" D2 cases still did not achieve MI < 5; D2 guided surgery "missed" some node stations at risk. Additionally, some D1 cases had MI < 5 either because of favorable characteristics of a particular tumor (e.g. favorable location, depth, size, histology) or because of documented "contamination," with tendency toward "D1.5" dissection.[11, 12, 21]

The management of splenic hilar nodes at station #10 represents a continued challenge for those desiring to plan and execute a "low Maruyama Index" operation. While pancreas-preserving dissection of #11 splenic artery nodes is feasible and recommended, [22, 23] especially when such nodes are at high risk per Maruyama Program, splenic preservation while dissecting splenic hilar nodes is problematic. Splenic resection appears to increase peri-operative mortality and may compromise long-term survival.[11, 15, 20, 24, 25] particularly in the elderly.[26] For this reason, neither splenectomy nor pancreatectomy are recommended, unless required to remove evident actual disease.

This blinded, retrospective analysis of Dutch Trial data suggests that "low Maruyama Index" surgery is associated with significantly increased survival. "Dose-response" with respect to Maruyama Index and survival is also apparent. We advocate using the Maruyama Program, a computerized tool based on actual patient experience, to identify nodal stations at risk, either preoperatively or intra-operatively, in order to customize surgical lymphadenectomy and routinely generate a "low Maruyama Index" operation. Our observations strongly suggest "dumping D " in favor of "low Maruyama Index surgery." Level I, prospective, randomized validation is the next step, and an international trial of this concept is currently being planned.

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5

Validation of a nomogram for predicting disease-specific survival following a R0 resection for gastric cancer

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ABSTRACT

A statistical model for predicting disease-specific survival in gastric cancer patients, based on a single US institution experience, was tested for validity in a different set of patients treated at different institutions. Four hundred and fifty-nine patients from the Dutch Gastric Cancer trial comparing D1 to D2 lymph node dissection, were analysed. Discrimination ability of nomogram with respect to 5 and 9 year disease-specific survival probabilities was superior to that of the AJCC stage. There was considerable heterogeneity of risk within many of the AJCC stages. Calibration plots suggested that predicted probabilities from the nomogram corresponded closely to actual disease-specific survival. The gastric cancer nomogram performed well when applied to patients treated in a large number of institutions. The nomogram provided predictions that discriminated better than AJCC stage, regardless the extent of lymph node dissection. Patient counselling and adjuvant therapy decision making should benefit from use of the nomogram.

INTRODUCTION

Although the incidence is declining in Western Europe(1), gastric cancer remains the second most common cause of cancer death worldwide.(2) Surgery is the only curative treatment. The influence of extent of gastric and lymph node resection is debated.(3-5) Adjuvant chemo-radiation has been proposed as well and tested in an attempt to improve local control and survival. The US Intergroup study by the Southwest Oncology Group showed a significant overall survival benefit after postoperative chemoradiation (36 versus 27 months median overall survival in the surgery alone-group), which lead to standardisation of this regimen in the United States.(6) The trial was criticized however for the suboptimal surgery employed and the level of unresected nodal disease. Surgical undertreatment, as observed in this trial, clearly undermined survival.(7)

Although treatment delivered determines patient's prognosis to a large extent, other factors such as patient characteristics, age and sex, the stage of disease at presentation, and tumour location and morphology play a substantial role. Current staging modalities, that solely focus on depth of tumour invasion and the presence of nodal disease, do not take these factors into account. Nomograms have been developed to address this problem: they are predictive

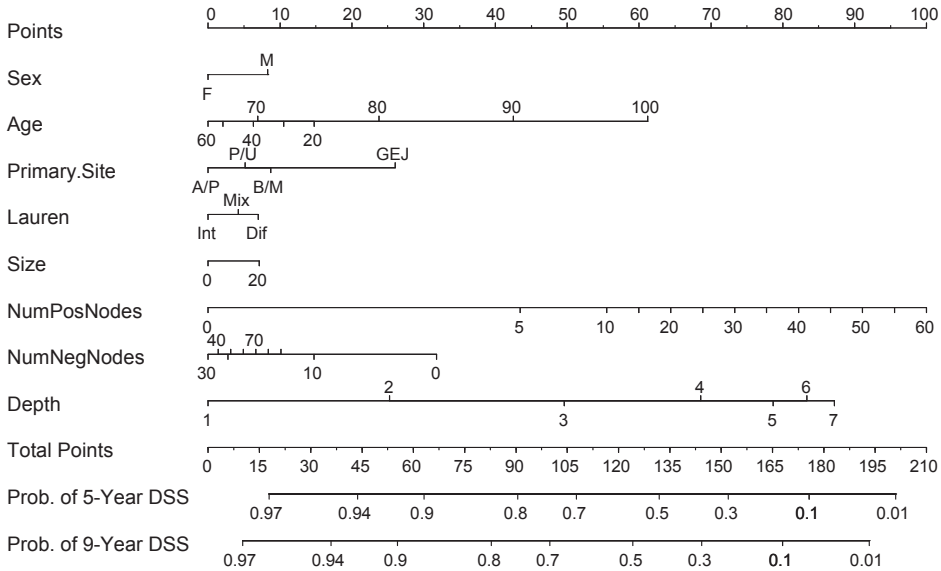

Figure 1. Nomogram for disease-specific survival

Instructions for Physician:
Locate the patient's sex on the **Sex** axis. Draw a line straight upwards to the **Points** axis to determine how many points towards gastric cancer-specific death the patient receives for his or her sex. Repeat this process for the other axes, each time drawing straight upward to the **Points** axis. Sum the points achieved for each predictor and locate this sum on the **Total Points** axis. Draw a line straight down to the disease-specific survival axes to find the patient's probability of surviving gastric cancer assuming he or she does not die of another cause first.

tools for the individual patient based on known prognostic variables including the extent of surgical treatment. Nomograms aid in patient counselling, follow-up scheduling and clinical trial determination and have been developed in soft tissue sarcoma(8), prostate(9-12), renal cell(13), pancreatic(14), and breast cancer.(15) The statistical model developed for gastric cancer (see figure 1) was able to predict the individual patient's probability for disease-specific 5 and 9 year survival after an R0 resection for gastric cancer in a single institution US patient population involving 1039 patients treated from 1985 to 2002.(16)

The purpose of this study was to assess the validity of this prediction tool when applied to patients with a different stage of disease at presentation, differing (surgical) treatment at different institutions. We also compared the discriminating value of the nomogram to the AJCC staging system.

PATIENTS AND METHODS

Patients were enrolled in the Dutch Gastric Cancer trial. This trial was undertaken between August 1989 and July 1993 and randomized gastric cancer patients, coming from 80 Dutch hospitals, between a limited (D1) and an extended (D2) lymph node dissection as recommended by the Japanese Research Society for the Study of Gastric Cancer.(17;18) The results of this trial have been published.(19-21) For the present analysis, patients were considered eligible if they had underwent an R0 resection, i.e. a resection with negative margins without any evidence of tumour spillage (n = 633). In agreement with our previous report, the following prognostic variables were assembled for use in validating the nomogram: age, sex, primary site (distal one third, middle one third, proximal one third, and gastroesophageal junction), Lauren histotype (diffuse, intestinal, mixed), number of positive lymph nodes resected, number of negative lymph nodes resected, and depth of invasion as defined by the standard nomenclature.(22) Patients with suspected vs. definite serosal invasion are distinguished in the nomogram. However, pathologic analysis from the Dutch trial did not distinguish between these depths. For purposes of nomogram validation, we calculated the nomogram prediction assuming a point half way between these two points on the nomogram. Patients with one or more missing values were excluded (Lauren histotype, n = 126; size, n = 19; primary site, n = 41), leaving 459 patients that had values for all nomogram predictor variables, AJCC stage, and follow-up. For each of these patients, the nomogram 5 and 9 year disease-specific survival probabilities were computed and compared with the AJCC stage on the basis of discrimination ability, as measured by the concordance index. Disease-specific survival was estimated using the Kaplan-Meier method.

Nomogram validation comprised two activities. First, discrimination was quantified with the concordance index.(23) Similar to the area under the receiver operating characteristic curve, but appropriate for censored data, the concordance index provides the probability

that, in a randomly selected pair of patients in which one patient dies before the other, the patient who died first had the worse predicted outcome from the nomogram.

Second, calibration was assessed. This was done by grouping patients with respect to their nomogram-predicted probabilities and then comparing the mean of the group with the observed Kaplan-Meier estimate of disease-specific survival. All analyses were performed using S-plus 2000 Professional software (Statistical Sciences, Seattle, WA) with the Design and Hmisc libraries added.(24)

RESULTS

Table 1 depicts the patient and tumor characteristics of the 459 eligible patients with all the information available for the nomogram calculation. With a median follow-up of 10 years, 194 of the 459 patients had died of disease. Disease specific survival by AJCC stage grouping is shown in figure 2, suggesting a reasonable number of patients alive at both 5 and 9 years for nomogram validation. The concordance index for the nomogram was 0.77. Calibration of the nomogram, as shown in figure 3, appeared to be accurate for both the 5- and 9-year predictions.

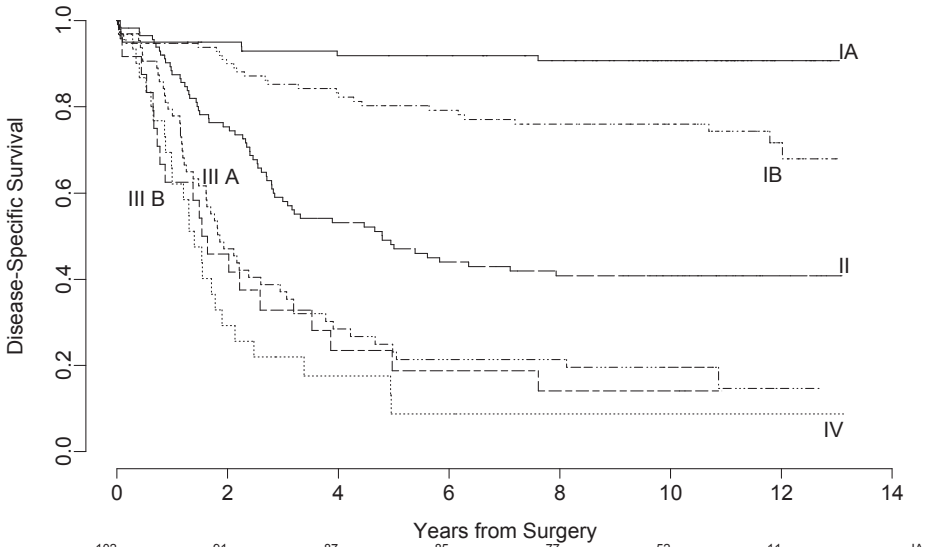

Figure 2. Disease specific survival by AJCC stage grouping

Table 1. Patient and tumor characteristics of all patients with available information on nomogram predictor variables

	N	%
Sex		
Male	270	59
Female	189	41
Primary Site		
A/P	199	43
B/M	191	42
GEJ	69	15
Lauren		
Mixed	17	4
Intestinal	337	73
Diffuse	105	23
Stage		
IA	102	22
IB	115	25
II	117	26
III A	69	15
III B	24	5
IV	32	7
Depth		
Mucosa	81	13
Submucosa	100	16
Propria musclaris	93	15
Subserosa	215	34
Suspected/definite serosal invasion	132	21
Adjacent organ involvement	12	2
Number of Negative Nodes		
Minimum	0	
1st Quartile	13	
Median	21	
Mean	24	
3rd Quartile	32	
Maximum	105	
Number of Positive Nodes		
Minimum	0	
1st Quartile	0	
Median	1	
Mean:	3.5	
3rd Quartile	5	
Maximum	28	
Size (cm)		
Minimum	0	
1st Quartile	3	
Median	4	
Mean	5	
3rd Quartile	6	
Maximum	24	
Age (years)		
Minimum:	31	
1st Quartile:	57	
Median:	66	
Mean:	64	
3rd Quartile:	73	
Maximum:	84	

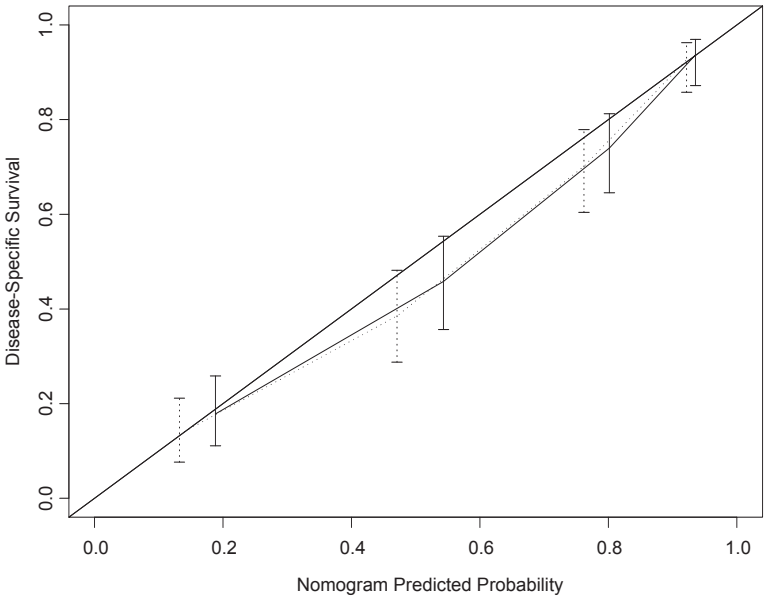

Figure 3. Calibration curves for the nomogram. X-axis is nomogram predicted probability. Patients were grouped by quartiles of predicted risk. Y-axis is actual disease-specific survival as estimated by the Kaplan-Meier method. Solid line is performance of the 5-year prediction; dotted line represents 9-year prediction. Vertical bars represent 95% confidence intervals. For each quartile of both nomogram predictions, the 95% confidence intervals overlap the diagonal "ideal" line, where predicted would exactly match actual disease-specific survival

We compared predictions from the nomogram with those obtained by using the AJCC stage groupings. Individual AJCC stage groups and nomogram predictions were compared for their ability to rank the patients (e.g. concordance index). Nomogram discrimination was superior to that of AJCC stage grouping (concordance index 0.77 vs. 0.75 $P < .001$, Z-test). This difference is difficult to appreciate clinically, and therefore, figure 4 illustrates the discrepancies between the two prediction methods. Within each AJCC stage grouping is a histogram of nomogram-predicted probabilities, illustrating heterogeneity within many of the stages.

DISCUSSION

Patient prognosis is currently estimated on the basis of AJCC staging, and not on other factors like age, sex or morphology that may have an impact on disease-specific survival. Integrating these variables in a nomogram has yielded a model that is a more accurate predictor for disease specific survival than is AJCC stage. This study validates the predictive value of the nomogram, previously tested in a single US institution.(16) The difference in concordance index between the nomogram and the AJCC staging is not great, and may therefore appear

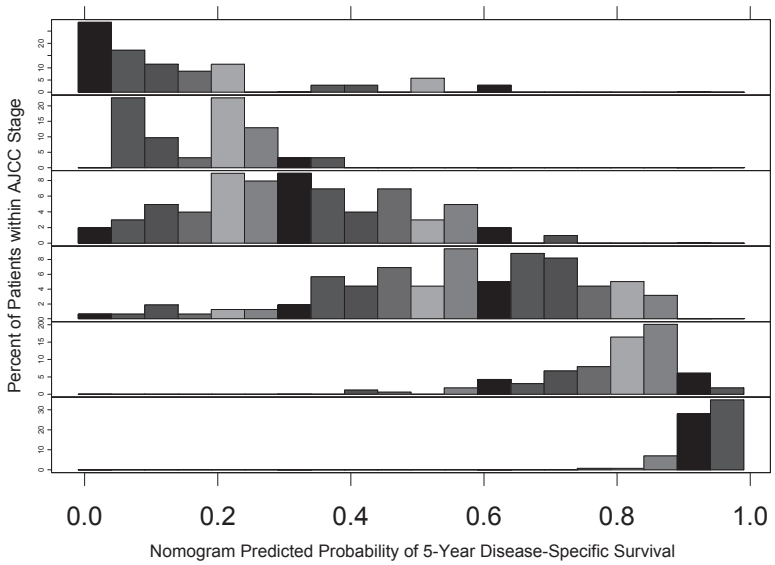

Figure 4. Nomogram predicted probabilities within each of the AJCC stages. Numbers in parentheses for each stage indicate number of patients within that stage. Note the large variation in nomogram predicted probability present within many of the stages

clinically irrelevant. However, figure 4 shows the clinical meaningfullness and benefits of nomogram predictions: patients within different AJCC stages with heterogeneous prognosis are successfully discerned, using the nomogram. Apparently, the present AJCC staging system is unable to identify subsets of patients with homogeneous prognoses. Accurate prediction can aid in individual patient counselling and in follow-up scheduling. It may also play a role in designing future trials, identifying subsets of patients within known AJCC stages that have a different prognosis, and likewise a potential for different response to novel adjuvant treatment regimens. It is important that this model, shown to be valuable in a single institution US patient population, is valid in a multicenter European gastric cancer patient population. The type of gastric cancer management depends largely on where the patient is being treated: many US gastric cancer patients receive postoperative chemoradiation(6), whereas adjuvant treatment is not the norm in Europe. In the current patient population as well as the original group of patients used to develop the nomogram, no adjuvant treatment was given, and the surgical treatment consisted of D1 and D2 dissection in all validation patients. This is more extensive surgery than undertaken in the general US patient population. The American College of Surgeons evaluated surgical treatment of over 18,000 gastric cancer patients between 1982 and 1987 and concluded that dissection of the celiac nodes occurred in only 14% of the cases.(25) Among the 3,804 patients having a curative resection, only 695 (18%) had dissection of the nodes along the celiac axis, hepatic artery, or splenic artery (N2 nodes).(26) Stage of disease differs between the current patient population and the US patients that were analysed in our previous report with less cases of advanced disease in the present

patient population because we included R0 patients only. Despite these major discrepancies between the series, the nomogram predicted accurately, superior to AJCC stage, for disease specific survival in a patient population treated in as many as 80 hospitals, consistent with common surgery in the Netherlands.

Patients in the present analysis were derived from the Dutch Gastric Cancer trial, comparing D1 to D2 dissection. The nomogram predicted well in this series despite the fact that type of dissection was not a variable, per se, in the nomogram. The likely reason for this favourable outcome is that the numbers of positive and negative nodes are predictor variables in the model. Thus far, there is still no overall difference in survival rates between the arms of the Dutch trial.(21) Consequently, considering the type of resection as an input variable for nomogram construction does not seem to have additional value. Defining the extent of lymph node dissection (i.e. D1 or D2) requires intra-operative identification of all 16 lymph node stations as defined by the Japanese Research Society for the Study of Gastric Cancer (JRSGC).(17;18) Identification and subsequent resection of all these separate stations may contribute to improving clinical outcome, even in Western patients considering recent publications that focus on adequate lymph node removal with critical organ resection, thus minimising postoperative morbidity and mortality.(27-29) Notwithstanding the efforts of improving locoregional control through extended nodal dissection, the surgical effort of meticulous dissection is not routinely performed in Western gastric cancer patients, especially not outside the framework of clinical trials. Including the type of resection as a mandatory input variable in the predictive nomogram would therefore make the nomogram less applicable in daily practise. However, the basis of the initial nomogram was an institution where extended lymph node dissection is performed in the majority, but not all, of patients. By requiring only the *numbers* of negative and positive lymph nodes resected for the nomogram computation without specifying their location, we believe that the extent of lymph node dissection is sufficiently addressed.

In conclusion, the gastric cancer nomogram performed well when applied to a validation dataset of patients, coming from a large number of institutions with different stage of disease, treated with a focus on lymph node clearance. The nomogram provided predictions that discriminated better than AJCC stages, regardless of the extent of lymph node dissection, and illustrated the heterogeneity of risk within many stages. With the availability of this external validation, individual patient counselling and tailored adjuvant therapy decision making should be encouraged using the nomogram, freely available in software from www.nomograms.org.

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6

Risk factors for anastomotic failure after TME surgery for rectal cancer

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ABSTRACT

Background: Anastomotic leakage is a major complication after rectal cancer surgery. We investigated risk factors that were associated with symptomatic anastomotic leakage after total mesorectal excision.

Method: Between 1996 and 1999 patients with operable rectal cancer were randomised between short-term radiotherapy followed by TME and TME alone. Eligible Dutch patients who underwent an anterior resection (n = 924) were retrospectivally studied.

Results: Leakage occurred in 107 patients (11.8%). Pelvic drainage and the use of a protective stoma were significantly associated with decreased anastomotic failure rates. A significant correlation between the absence of a stoma and anastomotic dehiscence was present in both male and female patients, and not only for distal, but also for proximal rectal tumours. In case of anastomotic failure, the presence of pelvic drains and a covering stoma were both related to a reduction in leaks requiring surgical reintervention.

Conclusion: It is recommendable to place one or more pelvic drains after TME to limit the consequences of anastomotic failure. A covering stoma is significantly associated with decreased anastomotic dehiscence and re-intervention rates in patients with both low and high rectal tumours, regardless their gender. The decision to construct a temporary stoma may be supported by this study.

INTRODUCTION

Symptomatic anastomotic leakage is the most important surgical complication following rectal cancer surgery. Leakage after low anterior resection can result in significant morbidity and mortality[1-5] and may be associated with a higher incidence of local recurrence[6-8]. Since the introduction of total mesorectal excision (TME) by Heald et al.[9], TME has become the accepted standard for rectal cancer surgery. The low recurrence rates and improved survival rates in TME series support the idea of removing the fatty tissue around the rectum, also known as the mesorectum[10-12]. However, concern has been expressed about the increased risk of symptomatic anastomotic leakage associated with the introduction of TME[13,14]. 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, TME potentially endangers the blood supply to the remaining rectum, thus jeopardizing anastomotic healing. Finally, removing the mesorectum leaves a large pelvic space for accumulation of a haematoma, which bears the risk of infection and sepsis. To avoid severe complications of anastomotic failure like peritonitis, septic shock and even death, it is crucial to take all possible measures to prevent symptomatic anastomotic dehiscence. The aim of this study was to identify risk factors for symptomatic anastomotic leakage in rectal cancer patients who undergo TME surgery.

PATIENTS AND METHODS

Study population

In the current study we used the database of the "Dutch TME trial", a large international multicenter trial that investigated the efficacy of short term preoperative radiotherapy (5x5 Gy) in TME treated rectal cancer patients. From January 1996 until December 1999 1861 patients with histologically proven adenocarcinoma of the rectum without evidence of distant metastases were included in the study and randomised between preoperative irradiation followed by TME surgery or TME alone. Patients were eligible for randomisation when the tumour was located below the level of S1/2 and 15 centimetres or less from the anal verge, being measured during withdrawal of a flexible coloscope. Also, the tumour had to be clinically resectable which meant that the tumour, on examination by the surgeon, was considered to be mobile and resectable without leaving behind any residual tumour (i.e. a R0 resection). Results of this trial have been published previously[15].

In the present retrospective analysis, only data that had been collected prospectively during the course of the TME trial were used. Only Dutch patients (n = 1530) were considered as data of only these patients regarding patient and treatment characteristics, as well as surgical complications and mortality, are complete and were checked extensively during trial accrual by the study coordinators[16].

Surgery

Within the context of the trial an extensive structure of workshops, symposia and instruction videos was set up to warrant optimal surgical quality and standardisation of TME technique[17]. In the protocol, the construction of a defunctioning stoma was recommended according to the surgeon's discretion, as well as the decision to drain the remaining pelvic cavity. In addition, a side to end or pouch anastomosis was advised, in an attempt to minimise the risk for anastomotic dehiscence. All surgical characteristics as well as operative and postoperative complications were recorded and completed on forms by the operating surgeon. These forms were compared with the operating report and discharge letters by the surgical trial coordinator and checked for inconsistencies. In case of unclear or incomplete data, additional information was requested.

Regarding the endpoint of this analysis, symptomatic anastomotic leakage was defined as clinically apparent leakage (i.e. gas, pus or faecal discharge from the pelvic drain, or peritonitis) or extravasation of endoluminal administered water soluble contrast on X-ray or CT-scan. An abscess around the anastomosis was also recorded as a leakage. Radiological examination was performed only in case of suspicion of anastomotic leakage.

Data Collection and Statistics

All case reports forms were sent to the central data centre in Leiden. After elaborate checking, data were entered in a database and analysed with SPSS statistical software (version 11.5 for Windows, SPSS, Chicago). Chi-square tests were used to compare proportions. A two-sided P-value of 0.05 was considered significant. The influence of independent variables on the risk of clinical anastomotic leakage was calculated using single variable regression analysis. All variables associated with leakage with $P < 0.1$ were entered in a multiple regression analysis. A P-value of 0.05 or less was considered significant.

RESULTS

Of all 1530 randomised Dutch patients, 1480 patients were eligible for enrolment into the clinical trial. Reasons for ineligibility were no adenocarcinoma (n=7), other/previous malignancy (n=26), previous treatment (n=3), transanal resection (n=1), double tumour (n=6), sigmoid carcinoma (n=5) and tumour not considered resectable at randomisation (n=2). Of all eligible patients 441 underwent an abdominoperineal resection, 78 patients a Hartmann procedure and in 37 patients no tumour resection was performed. The remaining 924 patients, who were evaluated in the present analysis, underwent an anterior resection according to the TME principle.

Five hundred seventy patients (61.7%) were male and 354 (38.3%) were female. Median age was 64.0 years (range 23-92). The average distance of the tumour from the anal verge

was 8.4 cm (range 0-18 cm). Four hundred and fifty nine patients (49.7%) were assigned to preoperative radiotherapy, the remaining patients to surgery alone. In 107 patients (11.8%) a clinical symptomatic anastomotic leakage was detected.

Patients who received pre-operative irradiation did not have an increased risk of anastomotic leakage compared to non-irradiated patients (10.9% versus 12.3%, P = 0.517). However, in irradiated patients the operating surgeon decided more often to construct a defunctioning stoma (59.9% versus 53.3%, P = 0.044).

A protective ileo- or colostoma was constructed in 56.6% of the patients. Eight point two percent of the patients with a stoma had a leakage compared to 16.0% of the patients without a stoma (P < 0.001). Leaving behind one or more pelvic drains after surgery was strongly associated with decreased leakage rates: in patients with pelvic drainage, anastomotic leakage was diagnosed in 9.6% of the patients, compared to 23.5% of the patients without a drain (P < 0.001). Male patients suffered more often from leakage (13.2% versus 9.0%) although this difference was not statistically significant (P = 0.057). The construction of a pouch was done in 261 patients. Patients with a pouch had a leakage rate of 8.4% compared to 12.4% in patients with an side-end anastomosis and 15.9% in patients with an end-end anastomosis (P = 0.092).

The correlation between tumour location and leakage rate was not significant: leakage rates for tumours 5 cm or less located from the anal verge, between 5.1 and 10 cm, and for tumours at more than 10.1 cm were 13.4%, 11.3% and 11.6% respectively (P = 0.872). However, if the tumour was located more proximally, a protective stoma was less often was constructed: faecal diversion was performed in 73.1%, 62.3% and 47.1% respectively (P < 0.001).

In the single variable regression analysis, a number of other continuous and dichotomous parameters were analysed that were possibly associated with clinical anastomotic leakage. The absence of a diverting stoma, the lack of one or more of pelvic drains left behind after surgery, male gender and the formation of an end-end or end-side anastomosis appeared to be significantly associated with the occurrence of anastomotic failure (table 1).

Multiple regression analysis was performed to exclude confounding due to interaction between the covariates. The absence of a defunctioning stoma and the lack of pelvic drainage remained the only two significant risk factors. Male gender was a non-significant risk factor with a P-value of 0.055 (table 2). The absence of a protective stoma was significantly associated with increased anastomotic dehiscence rates in both male and female patients (table 3). Moreover, this association is also present in patients with both low and high rectal tumours (table 3).

Management of symptomatic anastomotic leakage

Fifteen of the 107 patients (14.0%) with anastomotic leakage died within 30 days after surgery. Mortality related to anastomotic leakage did not differ significantly between patients with and without diversion (14.0% vs. 14.1%, P = 0.987), nor between patients with

Table 1. Single variable regression analysis of symptomatic anastomotic leakage. Values in parentheses are percentages. * n = 1 is missing. ** n = 6 missing. *** n = 7 missing. ETE: end-to end anastomosis. STE: side-to-end anastomosis

	Number of patients (%)	Relative risk	95% CI	P-value
Sex				
Female	32/354 (9.0)	1.00		
Male	75/570 (13.2)	1.53	0.99-2.36	0.059
Age		0.99	0.97-1.01	0.417
Distance tumour from anal verge				
≥10.1 cm	46/395 (11.6)	1.00		
5.1-10.0 cm	52/462 (11.3)	0.96	0.63-1.47	0.858
≤5 cm	9/67 (13.4)	1.18	0.55-2.53	0.676
Pre-operative radiotherapy				
Yes	57/465 (12.3)	1.00		
No	50/459 (10.9)	0.88	0.58-1.31	0.517
Intra-operative bleeding				
No	97/833 (11.6)	1.00		
Yes	10/91 (11.0)	0.93	0.47-1.87	0.853
Peroperative organ injury				
No	100/850 (11.8)	1.00		
Yes	7/74 (9.5)	0.78	0.35-1.75	0.553
Stapler*				
Double stapler	92/808 (11.4)	1.00		
No, hand-sewn	5/46 (10.9)	0.95	0.37-2.46	0.914
Single stapler	9/69 (13.0)	1.17	0.56-2.43	0.679
Type of reconstruction**				
Pouch	22/261 (8.4)	1.00		
ETE	17/107 (15.5)	2.05	1.04-4.04	0.038
STE	68/550 (12.4)	1.53	0.93-2.54	0.098
Diverting stoma				
Yes	43/523 (8.2)	1.00		
No	64/401 (16.0)	2.12	1.41-3.20	<0.001
Omentumplasty				
Yes	26/197 (13.2)	1.00		
No	81/725 (11.2)	0.83	0.52-1.33	0.431
Pelvic drainage				
Yes	76/792 (9.6)	1.00		
No	31/132 (23.5)	2.89	1.81-4.61	<0.001
Operation time***		1.00	0.99-1.00	0.942
TNM stage				
0	1/20 (5.0)	1.00		
I	31/285 (10.9)	2.32	0.30-17.93	0.420
II	29/230 (12.6)	2.74	0.35-21.26	0.335
III	38/345 (11.0)	2.35	0.31-18.07	0.411
IV	8/44 (18.2)	4.22	0.49-36.32	0.190

Table 2. Multiple regression analysis of symptomatic anastomotic leakage. Values in parentheses are percentages

	Relative risk	95% CI	P-value
Diverting stoma			
Yes	1.00		
No	1.89	1.24-2.90	0.003
Sex			
Female	1.00		
Male	1.55	0.99-2.42	0.055
Type of reconstruction			
Pouch	1.00		
ETE	1.70	0.85-3.41	0.135
STE	1.43	0.85-2.39	0.176
Pelvic drainage			
Yes	1.00		
No	2.53	1.57-4.09	<0.001

Table 3. Number of patients with symptomatic anastomotic leakage distributed according to gender, tumour location and the use of a protective stoma. Values in parentheses are percentages

	Diverting stoma	No diverting stoma	P-value
Gender			
Male	34/336 (10.1)	41/234 (17.9)	0.011
Female	9/187 (4.8)	23/167 (13.8)	0.003
Tumour location			
≤5 cm	4/49 (8.2)	5/18 (27.8)	0.040
5.1-10.0 cm	27/288 (9.4)	25/174 (14.4)	0.100
≥10.1 cm	12/186 (6.5)	34/209 (16.3)	0.002

or without pelvic drainage (11.8% vs. 19.4%, P = 0.310). Seventy nine patients underwent a surgical reintervention due to a (suspected) anastomotic failure: in 44 patients a diversion was constructed after all, in 8 patients an end-colostomy, 13 patients underwent a Hartmann procedure and in 14 patients the reintervention consisted of abscess drainage only. Fifteen out of 79 patients that had a surgical reintervention died as none died in the patient group without reintervention.

The need for surgical reintervention after detecting anastomotic failure was significantly lower for patients with pelvic drainage (56 out of 76 patients (73.7%) than for patients without drain (30/31, 96.8%, P = 0.006). A diverting stoma was also associated with lower rates of surgical reintervention as only 26 out of 43 patients (60.5%) with a stoma underwent surgery for the second time, compared to 60 out of 64 patients without a stoma (93.8%, P < 0.001).

DISCUSSION

In this large study population, symptomatic anastomotic leakage was detected in 11.8%, which is comparable with previous reports[1,12,13,18]. Before the start of the randomised trial, some surgeons expected increased surgical morbidity due to irradiation. In an earlier report it was shown that preoperative hypofractionated radiotherapy is a safe treatment without a rise in surgical complications[19]. There was no significant association between leakage and preoperative short term radiotherapy, which has become part of the standard regime for rectal cancer treatment in many European countries.

Data in the current analysis were derived from a prospective randomised trial that investigated the efficacy of short term preoperative radiotherapy in TME treated rectal cancer patients. The trial was not set up to answer any question regarding anastomotic leakage. Therefore, any statement based on data from the trial must be made most carefully. However, the performed analysis is informative and can identify risk factors for anastomotic leakage reliably.

In the multiple regression analysis, the lack of pelvic drains left behind after TME surgery, as well as the absence of a defunctioning stoma were the only two significant factors associated with anastomotic dehiscence. The possible acting mechanism of pelvic drainage and defunctioning in preventing clinical leakage can be explained biologically. After TME surgery, the large presacral space is a significant collector of fluids that may constitute an excellent medium for bacteria[20]. Infection of this haematoma may extend to, involve and drain into the anastomosis and cause dehiscence. The accumulation of these fluids is likely hindered by pelvic drainage. Nonetheless, several trials that investigated the usefulness of placing a drain after colorectal surgery do not favour pelvic drainage [21,22,22-25]. However, these trials often describe a heterogeneous population with either colonic[23,24] or colorectal resection[22,25] that did not undergo TME surgery[21,25]. Therefore, the results of these trials cannot be extrapolated automatically to TME treated rectal cancer patients. Also, the performed trials are often underpowered and hence not able to detect small differences that may be clinically relevant to both surgeons and their patients[22]. Furthermore, there are hardly any drawbacks from pelvic drainage: drains are easily left behind after rectal surgery and hardly burden the patient. Although not prospectively investigated, these data on TME rectal cancer patients suggest that it is recommendable to leave behind one or more pelvic drains after rectal surgery.

A covering stoma diverts the faecal stream from a healing anastomosis. In case of an anastomotic dehiscence, no faeces can be transported through a defective anastomosis into the abdominal cavity. In this way, the consequences of anastomotic failure are mitigated. It is generally accepted that low rectal anastomoses after TME are particularly vulnerable to anastomotic failure[1,26]. In the present series however, patients with both low and high rectal tumours were at substantial risk for anastomotic leakage and both patient categories may benefit from faecal diversion, as well as both male and female patients do. In this trial, the

decision to construct a defunctioning stoma was left to the discretion of the individual surgeon. Clearly, this decision is not solely made in an attempt to prevent leakage. Other factors, like the possible decreased quality of life after stoma formation[27], and the need to close a temporary stoma[28] play an important role as well. Indeed, temporary protective stomas tend to remain longer in situ than initially anticipated. In fact, after a median follow up of 5 years, 19% of the analysed patients with a so called temporary diversion, still has a stoma.

One possible important risk factor for anastomotic leakage is the performance of the individual surgeon[29-32]. This confounding factor is hard to measure but may be crucial. In this study population, it was examined whether each individual surgeon had a common policy of creating a protective stoma or placing pelvic drains when performing TME surgery on rectal cancer patients. There was a variable surgical strategy, i.e. most patients without pelvic drainage or a protective stoma were operated upon by surgeons who choose to place drains and divert the faecal steam in other patients, most likely based on intraoperative risk assessment of the likelihood of anastomotic dehiscence (data not shown). Thus, one could argue that patients with drains and a protective stoma would have a higher a priori risk of anastomotic dehiscence. This is however refuted by the present analysis, which strengthens the significant correlation between drainage, faecal diversion and lower rates of anastomotic failure.

In conclusion, the construction of a temporary stoma and the placement of one or more drains in the pelvic area are significantly associated with decreased anastomotic failure rates in rectal cancer patients treated with TME surgery. Moreover, these two measures are associated with a reduction in the rate of leaks requiring secondary surgery and thus with a mild clinical course in case of anastomotic dehiscence. In an attempt to minimise the risk of clinical leakage, stoma formation seems advisable, for patients with both proximal and distal rectal tumours, regardless their gender. However, individual patient characteristics have to be taken into account as well when deciding to construct a stoma. Considering the minimal burden to both patients and surgeons, we recommend placement at least one drain after TME for rectal cancer.

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Late side effects of short course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients. A report from the TME trial

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ABSTRACT

Purpose:

Preoperative short term radiotherapy improves local control in patients treated with total mesorectal excision (TME). This study was performed in order to assess the presence and magnitude of long term side effects of preoperative 5x5 Gy and TME. Also, hospital treatment was recorded for diseases possibly related to late side effects of rectal cancer treatment.

Patients and Methods:

Long term morbidity was assessed in patients from the prospective randomized TME trial, investigating the efficacy of 5x5 Gy prior to TME surgery for mobile rectal cancer. Dutch patients without recurrent disease were sent a questionnaire.

Results:

Results were obtained from 597 patients with a median follow up of 5.1 years. Stoma function, urinary function and hospital treatment rates did not differ significantly between the treatment arms. However, irradiated patients reported increased rates of fecal incontinence (62% vs. 38%, $P < 0.001$), pad wearing due to incontinence (56% vs. 33%, $P < 0.001$), anal blood loss (11% vs. 3%, $P = 0.004$) and mucus loss (27% vs. 15%, $P = 0.005$). Satisfaction with bowel function was significantly lower in irradiated patients, and the impact of bowel dysfunction on daily activities was greater in case of radiotherapy.

Conclusion:

Although preoperative short term radiotherapy for rectal cancer results in increased local control, there is more long term bowel dysfunction in irradiated patients than in patients who undergo TME alone. Rectal cancer patients should be informed on late morbidity of both radiotherapy and TME. Future strategies should be aimed at selecting patients for radiotherapy who are at high risk for local failure.

INTRODUCTION

Surgery is the key to cure for patients with rectal cancer. In the past, local recurrence rates after conventional surgery averaged 30% and varied considerably between institutions from 15% to 45%.(1-3) The acknowledgement of the importance of circumferential lateral spread in the occurrence of local failure(4) has led to the introduction of total mesorectal excision (TME).(5) This surgical technique ensures resection of the complete mesorectum in contrast to conventional blunt dissection which is known to leave behind fragments of mesorectal tissue, that frequently contain non-nodal foci of metastatic disease.(6) TME has proven its superiority with regard to local control and survival when compared to historical controls.(7-9)

Apart from surgery, the benefit of radiotherapy, either pre- or postoperatively given, has been established in several randomized trials as well.(10-15) The only randomized trial comparing pre- and postoperative radiotherapy clearly showed the superiority of preoperative radiotherapy regarding side effects and local control.(16) These results were confirmed in a large meta-analysis, including 8507 patients from 22 randomized trials, that concluded that preoperative radiotherapy is superior to postoperative radiotherapy in terms of cancer specific death (45% and 50% respectively, P=0.0003) and reduction of local recurrence risk (46% and 37%, P=0.002).(17) Furthermore, in the Swedish Rectal Cancer trial it was shown that a short-term regimen of high-dose preoperative radiotherapy (5x5 Gy) administered in one week was capable of not only reducing local recurrence rates (27 vs. 11%, P<0.001), but also improving 5 year overall survival (48% vs. 58%, p = 0.004) compared to surgery alone.(15)

The benefit of this radiotherapy regimen in combination with TME surgery was also suggested in the prospective randomized TME trial: after a median follow-up of 2 years, irradiated patients had lower local recurrence rates than patients who underwent radiotherapy alone (2.4% vs. 8.2%, P <0.001). No difference in overall survival could be detected (81.8% vs. 82%, P = 0.84).(18) In a previous report, reporting acute side-effects and complications of 5x5 Gy followed by TME surgery within one week, we showed that radiotherapy is a safe procedure despite a slight increase in complications when compared to TME alone.(19) While acute toxicity of short-term radiotherapy has been examined in several other trials as well(12;13;20), reports on long term morbidity are remarkably scarce. The aim of this study was to evaluate the effect of short-term preoperative radiotherapy and TME surgery on long term side effects in patients with operable rectal cancer.

PATIENTS AND METHODS

Study population

From January 1996 until December 2000, 1861 patients were randomized between preoperative radiotherapy (5x5 Gy) followed by TME and TME alone. Eligibility criteria for trial partici-

pation included histologically confirmed adenocarcinoma of the rectum without evidence of distant metastases. The inferior margin of the tumor had to be located not further than 15 centimetres from the anal verge and below the level of S1-2. Patients with fixed tumors were excluded as well as patients with locally treated (transanal resected) tumors.

Most patients (n = 1530) were Dutch. The remaining patients were included by Swedish, other European and Canadian centers. Only Dutch patients were considered in the present analysis as accurate collection and verification of data on late side effects was for logistical reasons feasible for these patients only. Secondly, only those patients were included who were present in the analysis of acute toxicity as well. In- and exclusion for this analysis has been reported previously.(19) Patients had to be free of local or distant recurrent disease in order to avoid confounding due to symptoms caused by disease recurrence. Finally, only those patients who had responded to the quality of life questionnaires, that were sent 18 and 24 months after surgery received a questionnaire about toxicity.

Treatment

Radiotherapy consisted of a total dose of 25 Gy given in 5 fractions over 5-7 days. A three or four-portal technique was used and the clinical target volume included the primary tumor and the mesentery containing the perirectal, presacral and internal iliac nodes up to the S1/S2 junction. The anal sphincter was included in the clinical target volume only if an abdominoperineal resection was planned. This resulted in an upper border at the level of the promontory, and lateral borders 1.5 cm over the pelvic inlet. In the lateral fields, the entire sacrum had to be included and the anterior border included the posterior part of the prostate or the vagina. Treatment was delivered with a three or four portal box technique, depending on the institutes' preference. The protocol prescribed an overall treatment time of at most 10 days. It was advised to give the radiotherapy on 5 consecutive days. Other details on radiotherapy have been described previously. (19)

All patients underwent surgery according the principles of TME surgery. Workshops, symposia and video instructions were organised to ensure quality controlled surgery. Moreover, in each participating center, the first five TME procedures had to be supervised by an instructing surgeon. Both radiotherapy and surgical procedures have been reported in detail in earlier instance.(18;20)

Measurements

Late morbidity was assessed using a questionnaire that was mailed to all patients in April and May 2003. The questionnaire was accompanied with a letter that explained the purpose of the study. In a pilot study, the questionnaire was tested for readability and understanding among 20 eligible patients. Patients that did not respond initially were sent one reminder. Table 1 shows the items of the questionnaire regarding bowel, stoma and urinary function. Patients could indicate the severity of dysfunction on a four-point scale ranging from "no, never" to

Table 1. Questions asked to assess bowel, stoma and urinary function

Bowel function
mean bowel frequency at day and night
anal blood and mucus loss
fecal incontinence at day and night
pad wearing due to fecal incontinence
Stoma function
peristomal skin irritation
stoma smell
stoma bleeding
stoma leakage
painful stoma
noisy stoma
Urinary function
mean urinary frequency at day and night
hematuria
dysuria
urinary incontinence
use of pads for urinary incontinence
need to urinate again within 2 hours
stream hesitation
difficulty to postpone urination
weak urinary stream
Impact of bowel and urinary dysfunction on
work or household activities
activities outside the house like shopping or paying visits
social activities like theatre or cinema visiting
Satisfaction with bowel, stoma and urinary function

"sometimes" (less than once a week), to often (more than once a week, but not every day) to "yes, always" (every day) for time dependent symptoms, and from "no, not at all" to "a little" to "pretty much" to "very seriously" for time independent symptoms. Data from four-point scale answers were transformed into binary outcome measures (i.e. signs yes/no present). Only if there were no complaints at all, the item was scored as not present. Level of satisfaction with bowel and urinary function was assessed using a 3 point verbal scale including "satisfied, neutral feelings, or unsatisfied". Because of previously reported neurogenic pain and subacute nerve damage using a fraction size of 5 Gy (21), questions regarding neurological function were included: patients were asked for the presence of back/buttock ache or pain in one or both legs, hip stiffness or pain, walking difficulties and the use of walking aids. In addition, patients were asked to rate their overall perceived health during the week prior to receipt of the questionnaire by means of a visual analogue scale (a 100 mm horizontal line, anchored at the extremes by 'best imaginable quality of life' and 'worst imaginable quality of life').(22)

Patients were further asked whether they were treated in the hospital (either on a in- or outpatient basis) since rectal cancer surgery for any of the following disorders: bowel obstruc-

tion, herniae cicatricales, delayed wound healing, anastomotic stenosis, stoma problems like parastomal hernia, stenosis and prolaps, chronic cystitis, fracture of hip and/or pelvis, and finally, myocardial infarction or stroke. Only those groups of diseases that were considered possible late side effects of treatment were specifically mentioned. In addition, patients were requested to report any other treatment in the hospital. Data on hospital treatment were added with information obtained from the regular follow-up of the TME trial.

Data Collection and Statistics

All questionnaires were sent to the central data centre in Leiden. Data were entered in a database and analysed with SPSS statistical software (version 11.5 for Windows, SPSS, Chicago). Chi-square tests were used to compare proportions. Student t-testing was applied for testing differences between continuous variables. A two-sided P-value of 0.05 was considered significant. No correction for multiple testing was applied.

RESULTS

Patients

Of all 1530 randomized Dutch patients, 116 were excluded for the assessment of acute radiotherapy toxicity.(19) These patients were also excluded for the present analysis. Other reasons for exclusion were death (n = 517), recurrent disease (n = 83) and no compliance with the completion of a previous quality of life questionnaire (n = 106). Thus, 708 patients remained evaluable. Median follow-up of these patients was 5.09 years since surgery and did not differ significantly between irradiated and non-irradiated patients. Of these patients, 597 returned the questionnaire, resulting in a response rate of 84%. Distribution of patients and clinical characteristics was well balanced between irradiated and non-irradiated patients as shown in table 2.

At the time of filling out the questionnaires, 362 patients did not have a stoma. Of these patients, mean bowel frequency during the day was significantly higher in irradiated patients compared to patients who underwent surgery alone (3.69 vs. 3.02, P = 0.011). Mean bowel frequency during the night did not differ statistically between the two randomisation arms (0.48 vs. 0.35, P = 0.207). Figure 1 shows significantly increased rates in irradiated patients of fecal incontinence at day and night, anal blood and mucus loss, as well as higher rates of pad wearing due to fecal incontinence. The severity of fecal incontinence for the two randomisation arms is shown in figure 2. Irradiated patients reported more signs of severe incontinence: daily incontinence was 5% in TME alone patients and 14% in irradiated patients. Figure 3 shows the degree of fecal incontinence depending on tumor distance from the anal verge: incontinence at day was significantly more reported after radiotherapy for patients with

Table 2. Clinical and pathological patients characteristics over both treatment arms. Of 1 one irradiated patient, tumor location was unknown

	RT+TME n=306		TME n=291		Total n=597
	n	%	n	%	Total
Age (mean, range)	63.06 (34-86)		61.60 (27-84)		
Sex					
male	199	65	170	58	369
female	107	35	121	42	228
Tumor location(*)					
≤5 cm	86	28	95	33	181
5.1-10.0 cm	123	40	109	38	232
≥10.1 cm	96	32	87	30	183
Operation type					
APR	91	30	86	30	177
LAR	200	65	197	68	397
Hartmann	15	5	8	3	23
TNM stage					
0	8	3	10	3	18
I	140	46	123	42	263
II	84	28	82	28	166
III	74	24	76	26	150
Stoma present					
No	177	58	185	64	362
Yes	129	42	106	36	235
Median follow-up (yrs)	4.98	2.6 – 7.6	5.18	2.7 – 7.5	5.09

tumors between 5 and 10 centimeters from the anal verge. The difference was not statistically significant for proximal lesions up to 15 centimeters.

More irradiated patients reported an impact of bowel dysfunction on daily activities like work and/or household (34% vs. 22%, P = 0.01) and activities outside the house (52% vs. 40%, P = 0.04). Although statistical significance was not reached, there was an increased impact on social activities (46% vs. 37%, P = 0.15) in irradiated patients.

Two hundred and thirty-five patients had a stoma at the time of completing the questionnaire. There were no statistical significant differences in stoma related difficulties although slightly more problems were seen in irradiated patients (table 3). Overall reported stoma complaints were 87% in irradiated and 82% in TME alone patients (P = 0.06). The impact of stoma (dys)function on work/household activities (31% vs. 33%, P = 0.77), activities outside the house (35% vs. 28%, P = 0.27) and social activities (35% vs. 28%, P = 0.29) did not differ significantly between the treatment arms, but was much lower than for patients without a stoma.

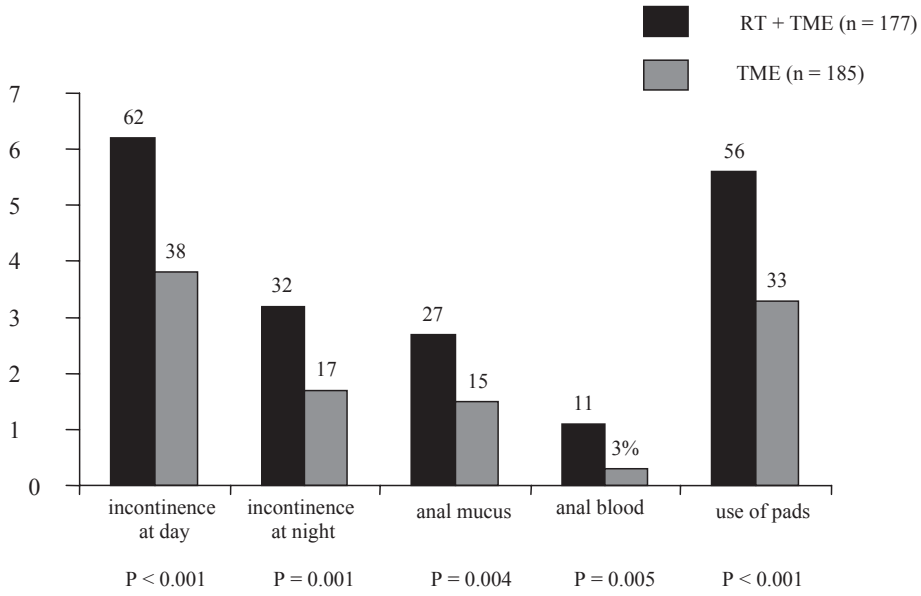

Figure 1. Bowel function in eligible patients at risk without a stoma

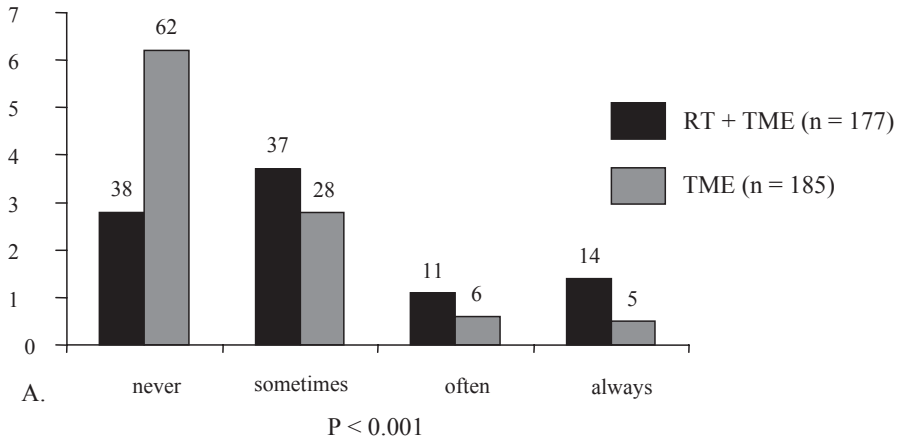

Figure 2. Degree of fecal incontinence at day in patients at risk without a stoma who reported some degree of fecal incontinence (n = 362). Sometimes was defined as once a week or less; often as more than once a week and always as every day

Patients with a stoma were more satisfied about their bowel functioning than patients without a stoma, whether they had received radiotherapy or not (figure 4). In stoma patients there was no difference in satisfaction between the randomization arms. In patients without a stoma, irradiated patients were less satisfied than non-irradiated patients (50% vs. 60%, p=0.008).

Table 4 summarizes results from urinary function assessment and shows no significant differences in voiding problems between the two treatment arms. However, around 39%

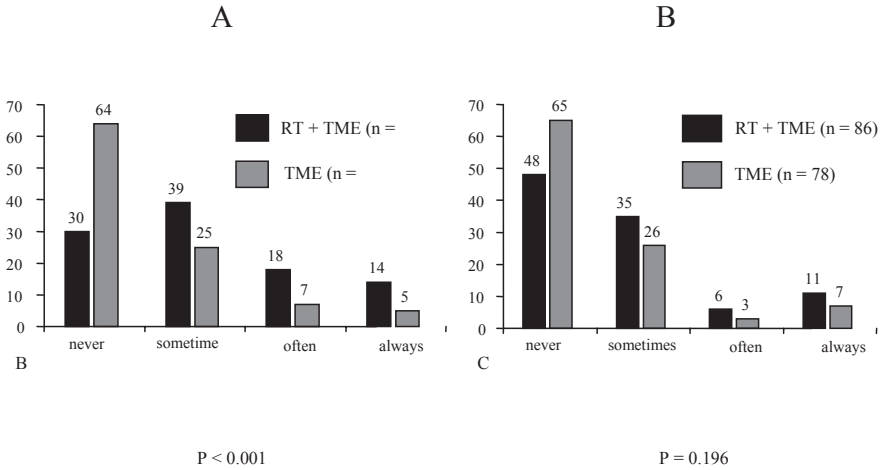

Figure 3. Degree of fecal incontinence at day in patients at risk without a stoma who reported some degree of fecal incontinence (n = 362) A. Patients without a stoma with tumors between 5.1 and 10 centimeters from the anal verge B. Patients without a stoma with tumors between 10.1 and 15 centimeters from the anal verge. Sometimes was defined as once a week or less; often as more than once a week and always as every day

Table 3. Stoma functioning in irradiated and non-irradiated patients

	RT+TME n=129			TME n=106			
	n	%	missing	n	%	missing	P-value
Peristomal skin irritation	48	39	5	32	31	4	0.251
Stoma smell	65	55	9	46	47	7	0.233
Stoma bleeding	45	39	12	34	34	7	0.531
Stoma leakage	34	30	14	23	24	8	0.317
Painful stoma	20	17	14	12	12	8	0.295
Noisy stoma	83	68	6	62	61	5	0.342
Any stoma problem	**110**	**87**	**2**	**82**	**78**	**1**	**0.063**
Impact on work/household activities	39	31	4	34	33	3	0.771
Impact on activities outside the house	44	35	2	29	28	2	0.271
Impact on social activities	42	35	9	28	28	7	0.289
Satisfaction about defecation							
satisfied	95	74		78	75		
neutral	30	23	1	22	21	2	0.783
unsatisfied	3	2		4	4		

reported to be incontinent for urine in both groups, and 57% of the patients wore pads due to urine incontinence.

There was no increase in the readmission rates in irradiated patients for the indications as displayed in figure 5. In particular, the number of cardiovascular accidents was not increased

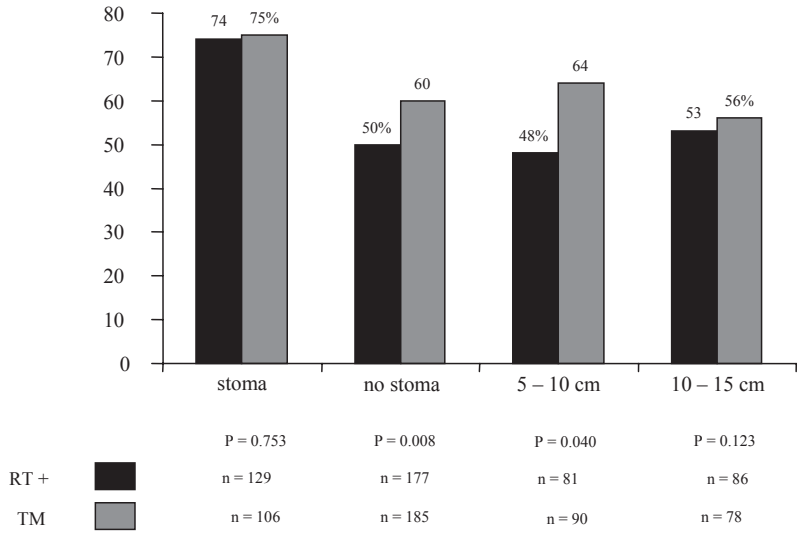

Figure 4. Proportion of patient subgroups that indicated to be satisfied with bowel function

Table 4. Urinary function

	RT+TME n=306			TME n=291			P-value
	n	%	missing	n	%	missing	
Median urinary frequency at day	6.21		21	5.97		11	0.270
Median urinary frequency at night	1.51		6	1.41		4	0.260
Hematuria	5	2	7	2	1	8	0.286
Dysuria	27	9	7	22	8	8	0.585
Urinary incontinence	118	39	6	109	38	3	0.711
Use of pads for incontinence	67	57	5	62	57	5	0.983
Sensation of uncompleted bladder emptying	139	47	13	134	48	9	0.985
Need to urinate again within 2 hours	203	70	16	195	71	18	0.710
Stream hesitation	131	45	15	136	49	13	0.315
Difficulty to postpone urination	152	53	17	141	52	17	0.788
Weak urinary stream	158	55	17	144	52	15	0.552
Need to push or stain to urinate	77	26	13	92	33	12	0.079
Satisfaction about urinary function							
satisfied	207	68		194	68		
neutral	74	24	6	75	26	5	0.903
unsatisfied	19	6		17	6		

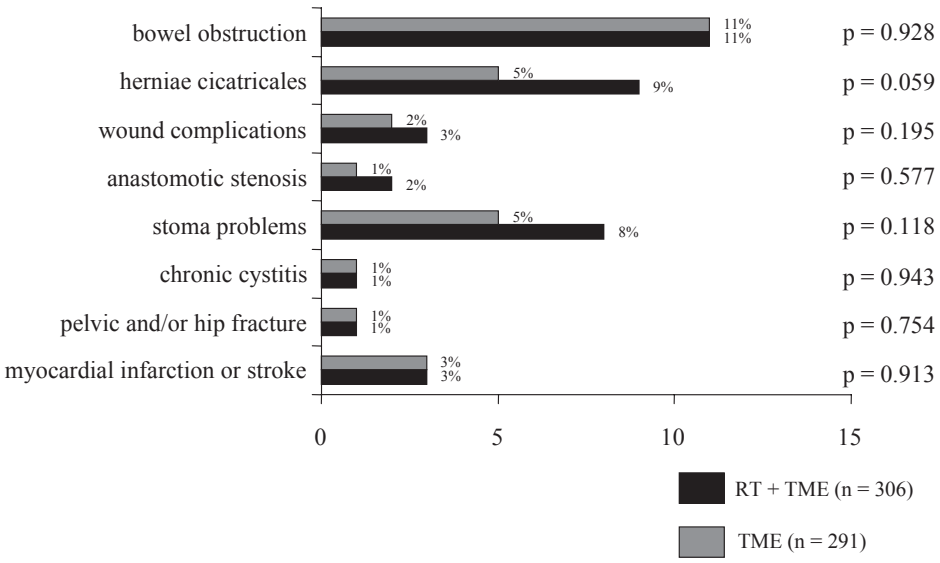

Figure 5. Rates of hospital treatment in all responding patients

in irradiated patients. Moreover, there were not more angina pectoris complaints after radiotherapy (12% vs. 16%, P = 0.17).

Back/buttock ache or pain in one or both legs was reported by 52% of the irradiated patients and 58% of the patients who underwent TME alone (P = 0.20). Hip stiffness or pain occurred in 34% of patients who underwent radiotherapy compared to 37% in case of TME alone (P = 0.423). Respective figures for walking difficulties were 43% and 46%, P = 0.79.

Median score on the visual analogue scale for overall perceived health was 82.0 for irradiated patients (range 13 – 100) and 81.0 for patients without radiotherapy (range 4 – 100) (P = 0.38). For patients with fecal incontinence, median VAS score was 79.0 (range 16 – 100) compared to 84.0 (range 13 – 100) for patients who were continent (P < 0.001). Of the continent patients, 68% was satisfied with their bowel function. For incontinent patients, this figure was still 44% (P < 0.001).

DISCUSSION

Short term preoperative radiotherapy has been successfully used to reduce local recurrence rates in TME treated rectal cancer patients.(18) This benefit of radiotherapy has to be balanced against the acute and late side effects of irradiation. We previously demonstrated that there is hardly an increase of acute toxicity after preoperative hypofractionated radiotherapy.(19) Concerning late side effects, there are only few reports available.(23;24) This study evaluated for the first time late sequela of radiotherapy and TME surgery within the framework of a randomized prospective trial. There were no significant differences in voiding and stoma

function, nor in symptoms possibly related to pelvic surgery or late side effects of radiotherapy. However, there were clear differences in bowel function between irradiated patients and patients who underwent TME alone.

In contrast to earlier radiotherapy studies (19;24), we detected no increased rates in irradiated patients of small bowel obstruction, urinary tract disease, femoral neck and pelvic fractures and arterial disease. The only randomized trial comparing pre- to postoperative radiotherapy, reported an increase in bowel obstruction in patients assigned to postoperative irradiation.(16) We now demonstrate that short-term preoperative radiotherapy does not lead to an increase in small bowel obstruction compared to surgery alone. This might be explained by the fact that in preoperative radiotherapy the pelvic cavity is still occupied by large bowel, thus creating a "natural spacer" for the small bowel, which consequently is not exposed to irradiation. This is in contrast to radiotherapy after pelvic surgery, in which case the small bowel descends into the small pelvis due to the created open space.

Also, there was no difference in the number of femoral head or pelvic fractures. This is in contrast with data from the Stockholm trials that showed 5.3% of femoral neck or pelvic fractures after radiotherapy, compared to 2.4% in patients without radiotherapy ($P = 0.03$)(24). In the Stockholm I trial, a two field technique was used that was replaced in the Stockholm II trial by a four-field box technique. Concomitant with this change in radiotherapy technique, there was a drop in the incidence of femoral neck and pelvic fractures. In our study, a three or four field technique was routinely used, which most likely explains the non-significant difference in fractures in our study population.

Long term urinary function was not deteriorated in irradiated patients compared to TME alone patients, which is in agreement with results from the Stockholm I and II trial, in which there was no statistical difference in urinary function between irradiated and non-irradiated patients. A small study (n=42) in male rectal cancer patients undergoing TME with or without preoperative radiotherapy demonstrated no significant difference in urinary function between irradiated and non-irradiated patients.(26) Although there is no statistical significant difference between both treatment arms in urinary incontinence rates, it is noteworthy to have incontinence reported in as much as up to 40% in both groups. One has to bare in mind however, that for the present study, loosing urine involuntarily once a week or less, was scored as urinary incontinence. Yet, there was an impact of urinary incontinence on overall perceived health: patients with urinary incontinence had a median VAS score of 77 (range 11 – 100) compared to 84 (range 4 – 100) for patients without urinary incontinence ($P < 0.001$).

Despite the undisputable improvements in radiotherapy technique and application in time, the adverse effect on long term bowel function and its impact on daily activities remains an important issue for concern. Dahlberg et al.(23) retrospectivally investigated the effect of preoperative high-dose radiotherapy in the Swedish Rectal Cancer Trial(15) and showed increased bowel frequency, incontinence, urgency and emptying difficulties in irradiated patients. In a recent report involving 124 patients undergoing anterior rectal resection, Welsh

et al.(27) showed higher incontinence scores in patients undergoing 5x5 Gy prior to TME. Data of these studies are in line with our results and indicate that there is price to pay for increased local control, even with adjusted radiotherapy technique. According to the TME radiotherapy protocol, the clinical target volume excluded the anal sphincter in case of an anterior resection with the lower border being 3 centimeters above the anal verge. Despite sparing of the anal sphincter, fecal incontinence rates were increased in irradiated patients. Apart from anal sphincter function, compliance of the rectal remnant is probably important for fecal continence as well. The latter might be decreased by radiotherapy due to aspecific changes in surrounding tissues.

As shown in figure 2, the proportion of patients expressing signs of fecal incontinence is considerable, especially in case of irradiation. Rates of fecal incontinence up to 62% in irradiated patients might appear unsurpassed when compared to previous studies. It needs to be stressed however, that even when the patient reported soiling once a week or less, the patient was considered as incontinent for the present study. Thus, comparison with previous reports should be made with care. Nevertheless, 14% of the irradiated patients mentioned to suffer from fecal incontinence every day compared to 5% of the TME alone patients, making the additional toxic effect of radiotherapy unnegligible.

Based upon subgroup analyses from the TME trial at a median follow-up of two years, radiotherapy is most effective for patients with tumors between 5.1 and 10 centimeters with local recurrence rates dropping from 10.1% to as low as 1.0% after preoperative radiotherapy ($P < 0.001$).(18) Figure 3 shows that the increase in incontinence rates due to radiotherapy is statistically significant in patients with mid-rectal carcinomas. This is not the case for patients with proximal lesions 10-15 centimeters from the anal verge. Thus, late term bowel dysfunction due to irradiation is more explicit in patients who seem to benefit most from radiotherapy.

It is not clear to what extent patients' quality of life is affected by impaired bowel function. In a concomitant study of our group, measuring health related quality of life on different time points up to 24 months after surgery, there were only few differences in quality of life between patients with and without preoperative radiotherapy, despite the presence significantly more fecal incontinence and sexual dysfunction in irradiated patients.(28) The current analysis of functional outcome was performed later in time and did not include a complete quality of life assessment. Nevertheless, overall perceived health was measured in this study: the median score of the Visual Analogue Scale was not significantly different between irradiated and nonirradiated patients without a stoma: 83.0 vs. 80.5 ($P = 0.374$), indicating that the increased rate of bowel dysfunction after radiotherapy is not expressed in a significantly worse VAS score for the whole population. However, we showed that impairment of bowel function had a significant effect on daily and social activities and this difference is translated in the overall perceived health, because the median VAS score was significantly lower for incontinent patients compared to continent patients (84.0 vs. 79.0, $P = 0.05$). In addition,

we demonstrated a statistical significant difference in satisfaction between irradiated and non-irradiated patients without a stoma: 50% vs. 60% respectively (P = 0.008).

We found no significant increase in stoma related problems in irradiated patients. In the analysis of acute radiotherapy toxicity, there was no increase of anastomtic dehiscence in irradiated patients.(19) Apparently, anastomotic bowel healing is not influenced by radiotherapy. In parallel to this finding, in the long run, stoma healing and function is neither affected adversely by radiotherapy. As shown in figure 4, irradiated stoma patients were satisfied with bowel function in 74% of the cases, versus 75% of non-irradiated patients (P = 0.753). Apart from the effect of radiotherapy, it is remarkable to note the distinction in satisfaction rates between patients with and without a stoma: patients reported to be satisfied with bowel function in 74% (n = 173) and 55% (n = 199) respectively (P < 0.001). Sphincter saving rectal surgery, often accompanied with long term bowel dysfunction, does not seem the ultimate goal that should be aimed for in every rectal cancer patient.

In conclusion, late term adverse effects of hypofractioned preoperative radiotherapy and TME surgery on functional outcome are considerable, using our strict criteria for dysfunction. However, an age-matched control group without a history of pelvic disease and treatment is lacking in the current study. Studying a control group, would possibly reveal a certain degree of dysfunction as well, making the real contribution of radiotherapy and surgery to functional outcome more clear. The results of our study, however, enable physicians to inform their patients reliably about the side effects of both radiotherapy and surgery in rectal cancer. Compared to radiotherapy, TME surgery is the main contributor to late bowel dysfunction. However, surgery is the only option that can lead to cure in contrast to radiotherapy that has merely benefits in terms of increased local control. The substantial additional long term side effect of radiotherapy on bowel dysfunction urges to tailor radiotherapy to those patients only who are most likely to benefit from it. In this way, unnecessary exposure to the described late side effects is avoided. However, pretreatment staging modalities presently used are incapable of identifying patients at risk for local failure accurately. Considering the significant increase in local control after preoperative radiotherapy for TME treated rectal cancer patients, 5x5 Gy remains a valuable treatment regimen.

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8

The randomized controlled TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma A report from the TME trial

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ABSTRACT

Objective. To investigate the efficacy of preoperative short term radiotherapy in patients with mobile rectal cancer undergoing TME surgery.

Summary Background Data. Local recurrence is a major problem in rectal cancer treatment. Preoperative short term radiotherapy has shown to improve local control and survival in combination with conventional surgery. The TME trial investigated the value of this regimen in combination with total mesorectal excision (TME). Long term results are reported after a median follow-up of 6 years.

Methods. 1861 patients with resectable rectal cancer were randomized between TME preceded by 5x5 Gy or TME alone. No chemotherapy was allowed. There was no age limit. Surgery, radiotherapy as well as pathological examination were standardized. Primary end-point was local control.

Results: Median follow-up of surviving patients was 6·1 years. Five year local recurrence risk of patients undergoing a macroscopically complete local resection was 5·6% in case of preoperative radiotherapy compared to 10.9% in patients undergoing TME alone ($P < 0{\cdot}001$). Overall survival at 5 years was 64·2% and 63·5% respectively ($P = 0{\cdot}902$). Subgroup analyses showed significant effect of radiotherapy in reducing local recurrence risk for patients with nodal involvement, for patients with lesions between 5 and 10 centimetres from the anal verge, and for patients with uninvolved circumferential resection margins.

Conclusions. With increasing follow-up, there is a persisting overall effect of preoperative short term radiotherapy on local control in patients with clinically resectable rectal cancer. However, there is no effect on overall survival. Since survival is mainly determined by distant metastases, efforts should be directed towards preventing systemic disease.

INTRODUCTION

For rectal cancer, surgery is the principal treatment leading to cure. In particular, surgical technique determines treatment outcome to a great extent. With the introduction of total mesorectal excision (TME) involving resection of the fatty tissue around the rectum, local control and survival rates have improved substantially.[1-3] In recent years, TME has become the standard in many countries and has replaced conventional blunt dissection that is known to leave behind mesorectal tissue, exposing patients to high risk of local recurrence and thus, poor survival.

Apart from the advances made in surgery, pre-or postoperative treatment has shown to be a significant contributor to improved local control and survival as well. The benefits of (chemo)radiation either given pre- or postoperatively have all been established in combination with conventional surgery.[4-13] The Swedish Rectal Cancer Trial showed that short-term high-dose preoperative radiotherapy (5x5 Gy) administered one week prior to surgery was capable of reducing 5 years local recurrence rates (27% vs. 11%, P < 0·001) and improving 5 year overall survival (48% vs. 58%, P = 0·004) compared to surgery alone.[14] The Dutch Colorectal Cancer Group initiated a large prospective randomized multicenter trial to investigate the efficacy of 5x5 Gy prior to TME. The Nordic Gastrointestinal Tumour Adjuvant Therapy Group and the European Organisation for Research and Treatment of Cancer (EORTC) participated in the trial. Surgical technique was standardized and quality-controlled in order to assess the value of radiotherapy in addition to TME reliably. Early results showed a reduced risk of local recurrence in irradiated patients at two years (2·4% vs. 8·2%, P < 0.001) without a difference in overall survival (82·0% vs. 81·8%, P = 0·84).[15] In this article, we report on the results of the TME trial after a median follow-up of 6 years with a focus on subgroup analyses.

METHODS

Patients with clinically resectable adenocarcinoma of the rectum without any evidence of distant disease were randomly assigned to preoperative radiotherapy using 5x5 Gy followed by TME or TME alone. Tumours had to be below the level of S1/S2 with the inferior tumour margin being 15 centimetres or less from the anal verge as measured during withdrawal of a flexible coloscope. Patients with previous treatment for rectal cancer were excluded from trial participation, as well as patients who had previous chemo- or radiotherapy to the pelvis. There was no age limit. Other inclusion and exclusion criteria have been reported previously.[16] Central and local ethics committee approval for the study was obtained as well as informed consent from included patients. Randomisation was performed centrally and based on permuted blocks of six, with stratification according to centre and the expected

type of surgery (i.e. low anterior resection or abdominoperineal resection). Primary endpoint was local control. The trial design was based on a local recurrence rate of 5% at 5 years in the radiotherapy group for patients who underwent a curative resection (e.g. a resection without microscopically involved resection margins) compared to 10% in patients assigned to surgery alone. Secondary outcome parameters included distant recurrence, overall and cancer specific survival. No interim analysis was planned or performed. Trial design, surgery and radiotherapy technique as well as pathology procedures have been described in detail elsewhere.[17-20]

The prescribed radiotherapy consisted of 25 Gy in 5 fractions delivered during 5 to 7 days. The clinical target volume included the primary tumour and its mesentery with vascular supply containing the perirectal, presacral and internal iliac nodes, up to the S1/S2 junction. A three or four portal "box" technique was recommended. The upper boarder was at the level of the promontory. The perineum was included in the treatment field only if the operating surgeon anticipated performing an abdominoperineal resection.

Surgery was scheduled to take place in the week after radiotherapy. Surgeons were taught to perform proper TME surgery through an extensive structure of workshops, symposia and video instruction. Also, a monitoring committee was installed to ensure adherence to the strict surgical protocol guidelines. The first five TME procedures in each participating hospital were supervised by an experienced instructor surgeon. The administration of concomitant or adjuvant chemotherapy was not allowed.

Pathologists were trained to identify lateral tumour spread according to the protocol of Quirke and Dixon.[19] A panel of supervising pathologists was installed to review the results of histopathological examination.[21]

Patients underwent clinical examination every three months during the first year after surgery and annually thereafter for the first two years after surgery. Liver imaging and endoscopy were mandatory. Local recurrence was defined as evidence of tumour within the pelvic or perineal area. Criteria for distant recurrence involved tumour growth in any other area, including the colostomy site or inguinal region. All recurrences were confirmed by one of the study coordinators by checking all original pathology and radiology reports.

Central data management was done at the Data Center at the Department of Surgery of the Leiden Medical University Medical Center, the Netherlands. Information from participating hospitals was collected on case report forms that were sent to the central office. Data were checked and entered in a database and analysed using the SPSS program (version 11.5 for Windows SPSS Inc, Chicago, IL). A two-sided P value of 0·05 or less was considered to indicate statistical significance. In accordance with our previous report, event-free times were recorded from the day of surgery until day of local or distant recurrence, or death, or day of last follow-up. Overall survival analyses comprised all eligible patients and were thus performed on an intention-to-treat basis. In accordance with our previous report[22], only patients who underwent a macroscopically complete local resection were included when calculating local

recurrence rates. Distant recurrence rates were based on all eligible patients who did not have distant metastasis at the time of surgery. Overall recurrence rate was calculated on the basis of the number of eligible patients who had a macroscopically complete local resection without distant metastasis at the time of surgery. Patient data were censored when at last follow-up contact the patient was alive or had no evidence of disease. The χ^2 test was applied to evaluate differences in proportions. Univariate survival analyses were carried out by the Kaplan-Meier method. The log-rank test was used for comparison of the Kaplan Meier curves. The Cox proportional hazard model was applied to calculate hazard ratios. All variables with a P-value of less than 0·10 were entered in a multiple regression analysis. For subgroup analyses, no adjustment for multiple testing was applied. Results of subgroup analyses have to be judged with care: any significant results must be viewed as generating hypotheses that require validation in subsequent studies. In case of subset analyses, a P value of 0·05 may not be accurate enough.

RESULTS

Recruitment of patients started in January 1996 and lasted until December 1999 with the enrollement of 1861 patients from 84 Dutch and 24 Swedish hospitals, as well as from 1 Canadian and 10 other European centers. Figure 1 shows characteristics for eligible and ineligible patients, as well as rates of complete local and distant resection, according to treatment arm.

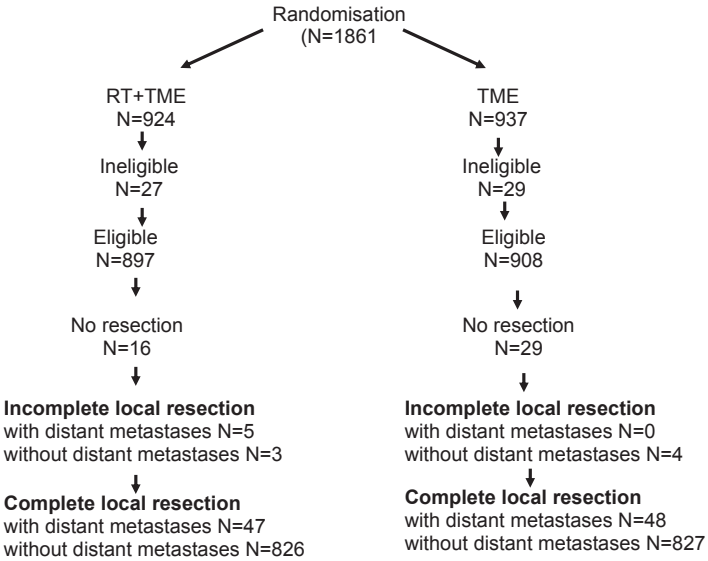

Figure 1. Numbers of eligible patients and extent of resection according to randomisation. (In)complete resection implies a macroscopic (in)complete resection.

Table 1. Patient and tumour characteristics according to randomisation of 1805 eligible patients*

	RT + TME		TME alone		P-value
	(n=897)	%	(n=908)	%	
Age (yrs)					0·79
Median	65.0		66.0		
Range	26 – 88		23 - 92		
Sex					0·92
Male	573	64	578	64	
Female	324	36	330	36	
Distance tumour from anal verge					0·37
≥10.1 cm					
5.1-10.0 cm	268	30	283	31	
≤5 cm	383	43	359	40	
Unknown	244	27	265	29	
	2	<1	1	<1	
Type of resection					0·11
None	16	2	29	3	
Low anterior	579	65	604	67	
Abdominoperineal	251	28	235	26	
Hartmann	50	6	39	4	
Unknown	1	<1	1	<1	
TNM stage					0·51
0	11	1	17	2	
I	264	30	243	27	
II	251	28	245	27	
III	299	34	325	36	
IV	62	7	61	7	
Unknown or no resection	10	<1	17	2	
CRM involvement					0·34
No	729	81	729	80	
Yes	143	16	148	16	
Unknown	25	3	31	3	

* Characteristics were unknown in some cases because not all case reports were received.

Fifty-six patients were considered ineligible after randomisation. Of these ineligible patients, 27 were randomized to receive radiotherapy prior to surgery, the remaining 29 patients to undergo surgery alone. Reasons for ineligibility in the radiotherapy arm were no adenocarcinoma (n = 5), tumour treated by transanal resection (n = 2), tumour location on more than 15 centimetres from the anal verge (n = 4), previous cancer (n = 8), coexisiting cancer (n = 4), previous large-bowel surgery, pelvic radiotherapy and/or chemotherapy (n = 2) and incomplete information on eligibility (n = 2). In the surgery alone arm reasons for ineligibility were no adenocarcinoma (n = 3), fixed tumour (n = 2), tumour location on more than 15 centimetres from the anal verge (n = 1), previous cancer (n = 13), coexisiting cancer (n = 7), previous large-bowel surgery, pelvic radiotherapy and/or chemotherapy (n = 1) and incomplete information

on eligibility (n = 2). Among the 1805 eligible patients, there were 139 patients with major protocol violations including no administration of the intended treatment (n = 54) or delivery of postoperative adjuvant treatment against protocol guidelines (n = 85). Minor violations included prolonged interval between the end of radiotherapy and surgery (n = 110) and non-compliance with the prescribed anatomical borders of the clinical target radiotherapy volume (n = 127). Specifics on major and minor protocol violations, as well as postoperative morbidity and mortality have been described before.[23] Patients with major and/or minor protocol violations were included in all the analyses. Table 1 shows patient characteristics that were well balanced across the treatment groups.

Forty-five eligible patients had no resection at all, 12 patients underwent a local resection with macroscopically involved resection margins (i.e. a local R2 resection). In 95 patients, distant metastases were diagnosed at the time of surgery or after randomisation with additional work-up (figure 1).

Follow-up was continued until November 2005. Median follow-up of surviving patients was 6·1 years (range 1·2 to 9·5 years) and did not differ between the two randomisation arms (6·0 vs. 6·1 years, P=0·760). Among 1748 patients who underwent a macroscopically complete resection, 129 patients had local disease recurrence. Of these patients, 83 (63·4%) patients had both local and distant relapse. Figure 2 shows Kaplan-Meier curves for relapse risk with

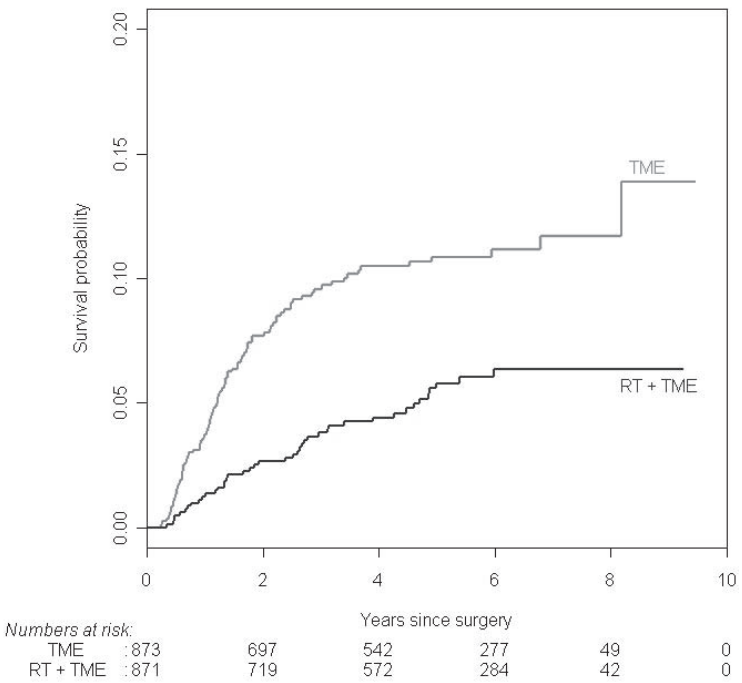

Figure 2. Rates of local recurrence among 1748 eligible patients who underwent macroscopically complete local resection, according to randomisation

Table 2. Univariate Cox regression analysis of local recurrence risk among 1748 eligible patients who underwent macroscopically complete local resection

	Hazard ratio	95% CI	P-value
Randomisation			<0·001
RT+TME	1·00		
TME alone	2·11	1·46 – 3·04	
Distance tumour from anal verge			0·001
≥10·1 cm	1·00		
5·1-10·0 cm	1·71	1·06 – 2·78	0·02
≤5 cm	2·44	1·50 – 3·95	<0·001
Type of resection			0·009
Low anterior	1·00		
Abdominoperineal	1·72	1·20 – 2·46	0·003
Hartmann	1·43	0·62 – 3·28	0·259
TNM stage			<0·001
I	1·00		
II	5·45	2·26 – 13·12	<0·001
III	13·61	5·94 – 31·20	<0·001
IV	22·60	8·44 – 60·57	<0·001
CRM involvement			<0·001
No	1·00		
Yes	4·03	2·82 – 5·76	

Table 3. Multivariate Cox regression analysis of local recurrence risk among 1748 eligible patients who underwent macroscopically complete local resection

	Hazard ratio	95% CI	P-value
Randomisation			<0·001
RT+TME	1·00		
TME alone	2·18	1·47 – 3·25	
Distance tumour from anal verge			0·031
≥10·1 cm	1·00		
5·1-10·0 cm	1·18	1·11 – 3·20	0·019
≤5 cm	2·31	1·16 – 4·64	0·018
Type of resection			0·942
Low anterior	1·00		
Abdominoperineal	1·06	0·60 – 1·89	0·839
Hartmann	1·15	0·49 – 2·69	0·751
TNM stage			<0·001
I	1·00		
II	4·08	1·65 – 10·09	0·002
III	9·92	4·25 – 23·16	<0·001
IV	20·26	7·43 – 55·28	<0·001
CRM involvement			<0·001
No	1·00		
Yes	2·16	1·46-3·19	

Table 4. Univariate log-rank analyses of 5 year local recurrence risk according to randomisation arm among 1748 eligible patients who underwent macroscopically complete local resection

	RT+TME		TME alone		P-value	P-value Interaction
	Number at risk	Local recurrence at 5 years	Number at risk	Local recurrence at 5 years		
Overall	873	5·6	875	10·9	<0·001	
Sex						0·943
Male	555	5·8	557	10·9	0·002	
Female	318	5·3	318	10·9	0·007	
Distance tumour from anal verge						0·032
≥10·1 cm	262	3·7	271	6·2	0·122	
5·1-10·0 cm	372	3·7	350	13·7	<0·001	
≤5 cm	237	10·7	253	12·0	0·578	
Type of resection						0·375
Low anterior	577	4·2	603	9·7	<0·001	
Abdominoperineal	248	9·2	232	13·4	0·147	
Hartmann	47	2·7	39	13·2	0·196	
TNM stage						0·659
I	265	0·4	244	1·7	0·091	
II	251	5·3	241	7·2	0·331	
III	298	10·6	324	20·6	<0·001	
IV	47	15·9	48	26·9	0·207	
CRM involvement						0·029
Yes	136	19·7	144	23·5	0·393	
No	715	3·4	717	8·7	<0·001	

local recurrence risk at five years being 5·6% in the group assigned to radiotherapy before surgery and 10·9% in TME alone patients ($P < 0·001$), implying a relative risk reduction of 49% in patients assigned to preoperative radiotherapy. In the univariate analyses (table 2), treatment group assignment, tumour location, type of surgery, TNM stage and circumferential resection margin (CRM) involvement were predictors of local recurrence risk. Multivariate Cox regression analysis revealed that randomisation arm, tumour location, TNM stage and (CRM) were independent predictors of local recurrence risk (table 3). Univariate log-rank analyses of 5 year local recurrence risk is displayed in table 4. According to these subgroup analyses, radiotherapy did not have a significant effect in patients with proximal and distal lesions, in patients who underwent a abdominoperineal resection or Hartmann procedure, nor in patients with TNM stage I,II or IV disease. However, interaction analyses in the Cox regression analysis between the respective covariates and randomisation revealed no significant interaction between type of surgery and treatment group assignment, nor between TNM

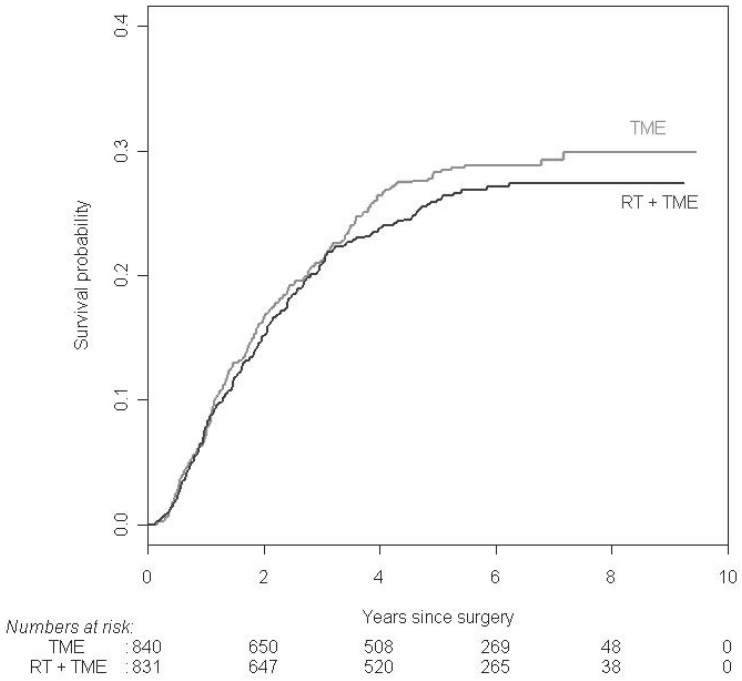

Figure 3. Rates of distant recurrence among all eligible patients who did not have distant metastasis at the time of surgery

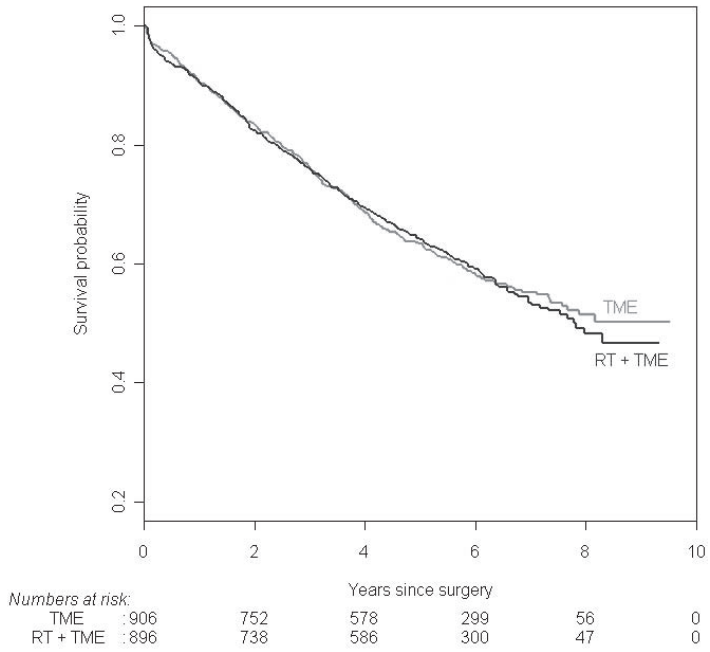

Figure 4. Rates of overall survival among 1805 eligible patients according to randomisation

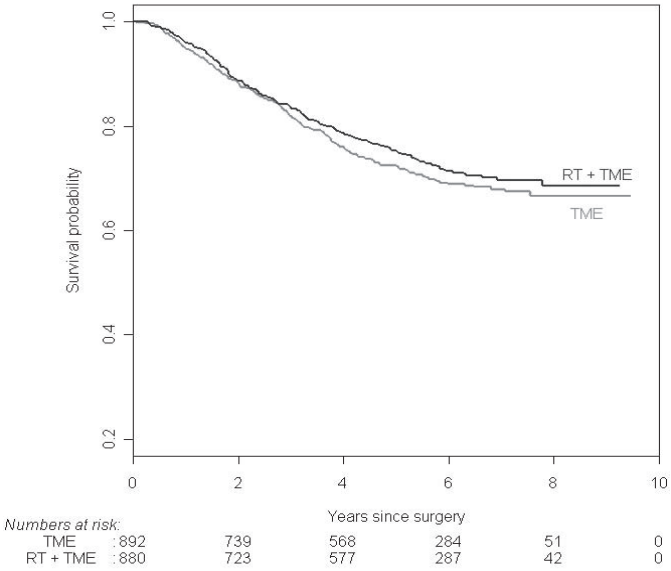

Figure 5. Rates of cancer specific survival among 1805 eligible patients according to randomisation

stage and treatment group assignment. This suggests that the effects of radiotherapy did not differ between these subgroups.

Distant recurrence was diagnosed in 201 cases that were assigned to radiotherapy compared to 222 patients in the surgery alone arm. Distant recurrence risk at five years was 25·8% and 28·3%, respectively (P = 0·387) (figure 3).

As of November 1st 2005, 748 patients had died. Of these patients, 374 (50·2%) died with recurrent disease. At five years, overall survival rates in irradiated patients were 64·2% which did not differ significantly from survival rates in patients who underwent TME alone (63·5%, P = 0·902, see figure 4). Respective cancer specific survival rates were 75·4% and 72·4% (P = 0·260) (Figure 5).

DISCUSSION

Short term preoperative radiotherapy results in improved local control for patients with resectable rectal cancer undergoing TME. Local control was chosen as primary endpoint in the present trial, since local recurrence is responsible for substantial morbidity and death. Local recurrence rates are significantly lower in irradiated patients, with a relative risk reduction of 49% when compared to TME surgery alone. This risk reduction at 5 years is smaller when compared to the relative risk reduction of 71% at a median follow-up of 2 years.[24] Figure 2 shows that a significant number of local recurrences occur beyond a follow-up period of 3 years in case of preoperative radiotherapy. This is in contrast to previously released data

that indicated that the majority of local recurrences become overt within three years after surgery.[25,26] In fact, in patients assigned to TME alone, only 9 (10%) out of 87 local recurrences appeared after 3 years of follow-up, compared to 13 (31%) out of 42 local recurrences in case of preoperative radiotherapy. Apparently, in a proportion of irradiated patients, radiotherapy does not prevent but merely postpones local recurrence. Hypothetically, radiotherapy decreases tumour burden, prolonging the time to macroscopically outgrowth. These results are in contrast to long-term follow-up data on the Swedish Rectal Cancer Trial where no delay was seen in irradiated patients.[27] In the Swedish trial, only a total 5 patients developed a local recurrence at 5 years after surgery. Four of these did not undergo radiotherapy. An explanation for this discrepancy might be the fact that, unlike the present trial, no TME was performed in the Swedish study. Conventional surgery results in a larger postoperative residual tumour burden that possibly needs less time to become apparent as a clinically recurrence.

In our study, increased local control in irradiated patients does not lead to a detectable improved overall survival. Although local recurrences are known to be an important cause of death, apparently, an absolute difference in local recurrence rates of 5·3% is too small to have a significant impact on survival. For comparison, in the Swedish Rectal Cancer Trial, an absolute reduction of 16% in local recurrence risk in irradiated patients (from 27% to 11%, $P < 0{\cdot}001$) was related to a significant improvement in 5 year overall survival (58% vs. 48%, respectively, $P = 0{\cdot}004$)[28], presuming local failure to be an important cause of death. In a recent survey of the Swedish Rectal Cancer Trial with a minimum follow-up of 14 years the difference in local recurrence rate is persistent (9% vs. 26%, $P<0{\cdot}001$) and this continues to improve overall survival after a long follow-up period (38% vs. 30%, $P = 0{\cdot}008$).[27]

In the recently published German randomized trial comparing preoperative to postoperative chemoradiation in patients with locally advanced disease, local recurrence rates were comparable to those of the current study (6% vs. 13% in favour of preoperative treatment, $P = 0{\cdot}006$). In parallel, there was no difference between the two randomisation arms in five year overall survival rates (76% resp. 74%, $P = 0{\cdot}80$).[29] Although trial results should be compared with care due to differences in case mix, it has to be noted that survival rates in the German study appear more favourable, despite the advanced stage of disease at presentation. However, the fact that as much as 18% of the patients, assigned to postoperative treatment turned out at pathological examination to have stage I disease, indicates that not only patients with locally advanced disease were included. Moreover, in the German study there was an upper age limit of 75 years excluding trial participation compared to no age limit in the TME trial. Differences in patient selection due to different staging techniques hinder adequate comparison of trial results. For example, the Polish trial comparing short term preoperative radiotherapy (5x5 Gy) to chemoradiation (50·4 Gy, 1·8 Gy per fraction plus bolus 5FU/LV) in patients with locally advanced rectal cancer accessible to digital examination, showed no difference in local recurrence risk (9% vs. 14%, $P=0{\cdot}17$)[30], despite the fact that there was more downsizing after prolonged treatment.[31] These results demonstrate that for the patients selected in this trial,

a short course of radiotherapy is at least as good as chemoradiation, indicating that not all patients with locally advanced tumours require a prolonged radiotherapy schedule. According to the EORTC 22921 trial, response rate is increased by the addition of chemotherapy to prolonged irradiation (14% vs. 5%, complete pathological response)[32], leading to a significant reduction in local recurrence risk (17·1% vs. 8·7% at 5 years).[33] This is in line with data from the FFCD 9203 trial that showed not only more complete responses after combined treatment (11·7% vs. 3·7%, P<0·001), but also a 2-fold reduction in local recurrence risk (16.5% vs. 8%, no P-value mentioned.[34] Although the addition of chemotherapy to radiotherapy seems justifiable on the basis of these data, acute and late toxicity may be more pronounced after combined treatment.

Discrepancies between trial results are most likely related to selection biases due to suboptimal staging, rather than to differences in biological behaviour. Preoperative clinical staging applying digital rectal examination and/or endorectal ultrasonography is increasingly replaced by magnetic resonance imaging, facilitating appropriate selection for the right type of neoadjuvant therapy.[35] Thus, the differences in patient characteristics between all these trials are difficult to appreciate, applying the current standards of local staging.

A potential advantage of prolonged neoadjuvant treatment over short term preoperative irradiation is tumour shrinkage and thus, sphincter preservation for distal rectal lesions. A prolonged overall time of irradiation, as well a protracted interval between radiotherapy and surgery is considered to be associated with downsizing, facilitating low-lying anastomosis. However, the aforementioned randomized trial comparing conventionally fractionated chemoradiation to preoperative short-term irradiation showed no difference in rates of sphincter preservation (58% vs. 61%, P = 0·57).[31] This might relate to the hypothesis that surgeons were reluctant to alter their initial surgical planning on the basis of response to neoadjuvant treatment. Sphincter preservation and thus, avoidance of a permanent stoma are thought to be of benefit for rectal cancer patients. However, in a recent study of our group investigating the late toxic effects of radiotherapy on functional outcome, patients with a (permanent) stoma were more satisfied with bowel functioning than patients who had undergone a low anterior resection and had no stoma.[36]

Clinical practise should not be based on the results of subgroup analyses: power is often too low to detect clinically relevant differences, and it is difficult to differentiate between subgroups prior to treatment. Nevertheless, subgroup analyses may be of interest for the development of future trials. According to the univariate analyses of local control (table 4), only patients with positive lymph nodes (i.e. TNM stage III) benefited from radiotherapy. Apparently, with the involved nodes having removed, preoperative radiotherapy is able to treat (microscopic) nodal disease beyond the plane of surgical resection. Lateral pelvic lymphadenectomy, as favoured in Japan[37-40] seems unnecessary with radiotherapy treating nodal spread sufficiently in a non-invasive manner. Preferably, patients with lymph node involvement are to be identified prior to treatment in order to avoid overtreatment. Although

the use of novel MRI contrast agents to predict nodal involvement prior to treatment seems promising[41], presently, the use of these agents is merely experimental and requires further investigation, especially for suspected nodes smaller than 5 millimeters.[42] Although subgroup analyses indicate a nonsignificant effect of radiotherapy for TNM stage I,II and IV, caution is warranted not to irradiate these patients considering the absence of significant interaction between TNM stage and treatment group assignment.

The efficacy of the investigated radiotherapy regimen depends on the location of the tumour: patients with proximal tumours do not benefit significantly from radiotherapy as becomes clear in table 3. Apart from the absence of a statistical difference, the number of events is rather low in patients with proximal lesions, making the number of patients needed to treat to prevent one local recurrence considerably high. Surprisingly, in the aforementioned German trial, there is no difference in local relapse risk between patients with tumours in the middle and upper part.[43] Possibly, the completeness of mesorectal excision that might be less in case of proximal lesions is an explanatory factor. For patient with low tumours up to 5 centimetres from the anal verge, there is neither a significant effect to the benefit of short course irradiation. This contradicts data from the Swedish Rectal Cancer Trial that showed an effect of radiotherapy for this group of patients.[27] Also, the Swedish Rectal Cancer Register has demonstrated a significant effect on local recurrence rates by applying 5 x 5 Gy preoperatively for patients with low lying rectal cancer. (Swedish Rectal Cancer Register (2004) http://www.SOS.se/mars/kvaflik.htm (Swe). A possible important confounding factor for this patient subset is the substantial proportion of patients with positive CRM involvement. Unfortunately, Swedish data on margin involvement are not available, but hypothetically, CRM involvement occurs less often in Sweden. Especially for patients with distal lesions, incomplete resection constitutes a major problem: as shown earlier, positive CRM is the most important independent predictor for local failure.[44] Table 4 shows unacceptable high rates of local recurrence in case of positive CRM. For these patients, radiotherapy has no significant effect (19·7% vs. 23·5%, P = 0·393). In particular, for patients requiring APR, complete resection seems a major challenge: in this subgroup, as much as 30% had involved CRM compared to 11% of the patients undergoing LAR ($P < 0.001$). Hypothetically, a cylindrical resection in stead of "coning in" towards the distal margin is appropriate in an attempt to avoid incomplete resection. Alternatively, as mentioned before, prolonged (chemo)radiation may result in downsizing facilitating curative resection. Again, speculations based upon subgroup analyses require validation in future studies. Precise tumour location is often difficult to assess prior to treatment: discrepancies between coloscopy measurements, CT and MRI imaging and intraoperative findings are often encountered and indicate the difficulty of determining exact tumour position and the a priori chance of local failure. Therefore, these subgroup analyses provide limited support to withhold radiotherapy from patients with proximal rectal cancer or to apply a prolonged radiotherapy schedule for patients with distal rectal cancer.

In conclusion, with increasing follow-up, there is still a highly significant effect of short term preoperative radiotherapy on local recurrence rates. There is no detectable effect on overall survival. TME surgery contributes significantly to superior local control and survival compared to results from conventional blunt dissection. Future efforts should be directed towards optimal preoperative imaging in order to differentiate between rectal cancers where a free CRM can be obtained or not. In the latter a more aggressive approach is warranted. In the future, adjuvant chemotherapy might gain a role for patients with clinically resectable rectal cancer in an attempt to improve survival, now that local treatment has been optimised by both TME and short term preoperative radiotherapy.

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9

Benchmarking the treatment of locally advanced rectal cancer: a comparative analysis of combined modality treatment with the Dutch randomized TME study

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ABSTRACT

Introduction

Objective of this article is to evaluate the current multimodality treatment for locally advanced rectal cancer (LARC) and to gain more insight in tumour biology.

Patients

A group of 201 single institution multimodality treated LARC patients with T4 and T3 tumours growing less than 2 mm from the mesorectal fascia were compared with a second group consisting of 316 patients with a T3 resectable rectal tumour, included in the Dutch TME trial.

Results

Overall survival after 3 years was not different (76% for TME, 67% for LARC, p = 0.071). Local recurrence rate (LR) was significantly lower in TME patients than in LARC patients at 3 years: 5% and 17% (p = 0.0001). In 83% of the LARC patients a negative circumferential resection margin could be realised, compared to 75% of the TME patients (p=0.037). Both circumferential margin status and lymph node status were important outcome parameters in both groups.

Conclusion

In both groups circumferential margin involvement and nodal positivity are independent prognostic factors in local control and survival. Outcome for a LARC patient is similar to resectable TME patients in absence of these factors. However, when chemoradiation did not result in achieving tumour regression and subsequent negative resection margins and negative lymph nodes, prognosis of LARC patients is significantly worse.

INTRODUCTION

For planning of surgical treatment, rectal carcinomas growing through the muscularis propria of the bowel wall (tumour invasion classification T3), are the most difficult group, since these are inhomogeneous. A large majority of these tumours present themselves as mobile at rectal examination. Mobility is considered a surrogate for the probability of freedom of involvement of the circumferential margin (CRM). These tumours can adequately be treated with short-term preoperative radiotherapy (5x5 Gy), followed by Total Mesorectal Excision (TME). However, a small proportion of T3 tumours infiltrate into or nearly into the circumferential fascia, and even with appropriate performed TME surgery free circumferential margins are not likely to be obtained. As these tumours are often less mobile at rectal examination, they are often referred to as being fixed. Fixity is a subjective measure, and cannot always be assessed properly. Infiltration into the vaginal septum or seminal vesicles may be underestimated at rectal examination and the same accounts for tumours out of the reach of the palpating finger. Large tumours may be over-staged merely due to their physical dimensions. The development of the Magnetic Resonance Imaging (MRI) has made it possible to distinguish a likely involved or free CRM (1, 2). In this paper locally advanced rectal cancer (LARC) refers to the close relation of the tumour to the circumferential margin based on MRI.

The treatment of patients with LARC is difficult. Short-term radiotherapy, followed by immediate surgery, does not result in down-staging of tumours (3) and is not effective in patients with a positive CRM (4). A positive CRM has been repeatedly showed to be one of the most important prognostic factors for local recurrence, next to invasion depth and nodal status in both mobile and LARC tumours (5-9). This has led to the development of neoadjuvant multimodality treatments with preoperative downsizing as main goal, in order to help the surgeon to achieve a radical resection.

Recently, several multimodality strategies have been investigated, but controversies remain to exist. At present, practice differs in Europe and in the USA, between countries in Europe, and even between institutions within the same country. It is obvious that current results are superior compared to historical controls. However, large differences in patient selections and treatment strategies make interpretation of the results difficult.

The current study compares the mobile or "not locally advanced" rectal cancer patients, treated with short-term radiotherapy with LARC patients, treated with long term (chemo)radiation. Prognosis, as well as known prognostic factors were compared.

PATIENTS AND METHODS

LARC group

The Catharina Hospital in Eindhoven is a national referral centre for rectal cancer patients in whom a R0 resection is not likely to be obtained. Multimodality treatment of patients with primary locally advanced rectal cancer is applied since 1994 (10). This study group consists of 201 consecutive patients with locally advanced primary rectal adenocarcinoma treated in the Catharina Hospital Eindhoven between 1994 and 2004. Patients presenting with a rectal tumour infiltrating into the mesorectal fascia or within proximity of less than 2 mm on MRI were eligible. Most of these tumours were referred as being fixed at rectal examination. Sometimes fixity was established by bimanual palpation during a staging laparotomy. All patients had biopsy-proven rectal adenocarcinoma. Patients with recurrent rectal cancer and distant metastasis at first presentation were excluded. The data were collected prospectively. Mean age was 62,1 years (36-86 years), 122 patients were male and 79 female. Median follow up of the survivors in this group was 36 months. The first 71 patients were treated with long course of preoperative radiotherapy consisting of 50,4 Gy (1,8 Gy fraction). Later, chemotherapy was added to the radiotherapy. In 109 patients daily bolus injections 5FU 350 mg/sqm and leucovorin 20 mg/sqm were administered two hours before irradiation in the first and fifth week of irradiation. In 2003 21 patients received a continuous scheme: 825 mg capecitabine/sqm bid every irradiation day and oxaliplatin 50 mg/sqm every first day of each irradiation week, total irradiation dose 45 Gy/1.8 Gy fractions in five weeks. After 6-8 weeks patients underwent radical surgery. During this surgery intraoperative radiotherapy (IOERT; 10-15 Gy) was applied as a boost at the area of risk. Details about this procedure were published before (10). Standard pathological analysis was performed on all rectal resection specimens.

TME study group

Data from patients included in the Dutch TME trial were the basis of this study. The TME trial is a large prospective randomized multicentre trial that compared short term (5x5 Gy) preoperative radiotherapy and TME surgery with TME surgery alone which has been extensively described (11, 12). Informed consent had been obtained from all included patients and the medical ethics committees of all participating hospitals have approved the trial.

For the current study, data of the eligible Dutch patients in the trial as described earlier were analyzed (11) . The following patients were excluded from the analysis: no resection, tumour left behind, distant metastases at operation, TNM stage IV and no tumour at operation. For the current analysis, patients with pT1 or pT2 tumours were also excluded. Of the remaining patients only those who were randomized to the arm with 5x5 Gy preoperative irradiation (n=316) acted as benchmark, since these patient represent optimal standard treatment in the Netherlands. Mean age was 63,2 years (26-88 years), 214 patients were males and 102 were

females. Accrual for the TME study was from 1995 until 2005 and the mean follow up of the survivors at the time of analysis was 58 months

Statistics

Patient characteristics were compared using the chi-square test. Prognosis (overall survival (OS), distant metastasis free survival (MFS) and local recurrence free survival) were calculated, using the Kaplan-Meier method. Log rank testing was used to compare these different patient groups. The starting point for the analyses of survival and recurrence was the day of surgery.

Multivariate proportional hazard regression analysis (Cox regression) was performed to identify independent risk factors for the primary outcome variables, using the parameters with a p-value of less than 0.05 in the univariate analysis. A prognostic model for the outcome parameters was built, incorporating the significant variables. Data have been analysed with SPSS statistical software.

RESULTS

Univariate survival analysis

Table 1 shows the survival characteristics of CRM involvement, lymph node involvement and surgical procedure in the LARC population and irradiated patients of the TME trial. In T3-LARC and T4-LARC patients a similar outcome was observed in all investigated variables, therefore LARC patients will be reported as one group.

Prognosis in both patient populations was similar for OS en MFS (figure 1). However, the local recurrence rate (LR) was significantly lower in TME patients than in LARC patients at 3 years: 5% versus 17% ($p = 0.0001$). In contrast, more positive CRMs were present in the TME group (25% versus LARC 17%, $p = 0.037$). In patients with negative margins, local recurrence rates were 2% (TME) versus 10% (LARC); in patients with positive margins 14% (TME) versus 53% (LARC), $p < 0.0001$. Figure 2 shows the influence of positive margins on local recurrence for both the TME and LARC patients. Nodal status was an important prognostic parameter. In patients with negative lymph nodes local recurrence rates after 3 years were 3% (TME) versus 12% (LARC, $p = 0.004$). In patients with positive nodes: 7% (TME) versus 28% (LARC, $p = 0.0007$). Development of metastases and overall survival were predicted by nodal status as well, but there were no differences between both patient populations (figure 3).

Type of surgery and location of the tumour:

With a tumour below 5 cm from the anal verge 20% of the patients underwent a low anterior resection (LAR) and 80% an abdomino-perineal resection (APR). Irrespective the location of the tumour AP resected specimens showed significantly more positive circumferential margins (31% versus 15%, $p<0.0001$). When TME patients were compared to LARC patients, the

Table 1. Kaplan-Meier (log-rank) Univariate calculated 3 year survival analysis

			Overall survival			Local recurrence			Distant metastasis free survival		
	TME	LARC	TME	LARC		TME	LARC		TME	LARC	
	n	n	3yr % (n)	3yr % (n)	*p*	3yr % (n)	3yr % (n)	*p*	3yr % (n)	3yr % (n)	*p*
All patients	316	201	76% (232)	67% (75)	0.0706	5% (227)	17% (73)	0.0001#	69% (191)	67% (59)	0.2337
CRM neg	238	167	81% (188)	74% (66)	0.1103	2% (184)	10% (65)	0.0096#	77% (162)	70% (54)	0.0519
CRM pos	78	34	60% (44)	40% (9)	0.1180	14% (43)	53% (8)	0.0000#	44% (29)	51% (6)	0.9844
p			0.0000#	0.0002#		0.0001#	0.0000#		0.0000#	0.0143#	
LAR	220	97	77% (166)	69% (35)	0.1968	2% (163)	18% (34)	0.0000#	72% (138)	62% (27)	0.0601
APR	96	90	73% (66)	70% (33)	0.3293	12% (64)	15% (32)	0.5811	63% (53)	69% (25)	0.9694
p			0.7149	0.7015		0.0022#	0.8138		0.2905	0.5735	
pN neg	166	132	84% (135)	75% (52)	0.0999	3% (131)	12% (51)	0.0042#	85% (120)	77% (41)	0.0611
pN pos	150	69	67% (97)	54% (23)	0.0629	7% (96)	28% (22)	0.0007#	52% (71)	49% (18)	0.2319
p			0.0000#	0.0025#		0.0044#	0.0163#		0.0000#	0.0000#	

CRM: circumferential resection margin, LAR: low anterior resection, APR: abdomino-perineal resection, pN: pathological lymph node status, # significant (log rank < 0.05)

latter had significantly less positive margins after APR (43% vs 19%, p=0.0001). In contrast, after LAR there was no significant difference between the two patient groups (LARC 10% vs TME 17%, p= 0.133). Overall survival and metastases-free survival were similar in both treatment groups, if stratified for surgical technique. However, LR-rate for LAR patients was much lower in TME patients than in LARC patients: at 3 years 2% versus 18% (p=0.000).

Multivariate analysis.

Table 2 summarizes the results of the Cox regression multivariate analysis. The location of the tumour and the type of operation showed no longer prognostic value. Nodal status, CRM and patient population remained important factors for prognosis.

Based on these results we created four prognostic groups for each patient population (table 3, figures 4a, 4b, 4c). These figures illustrate the good prognosis of LARC patients in case of a negative CRM and negative lymph nodes. The TME patients with both positive lymph nodes and a positive CRM show a poor prognosis, just like the LARC patients with these characteristics.

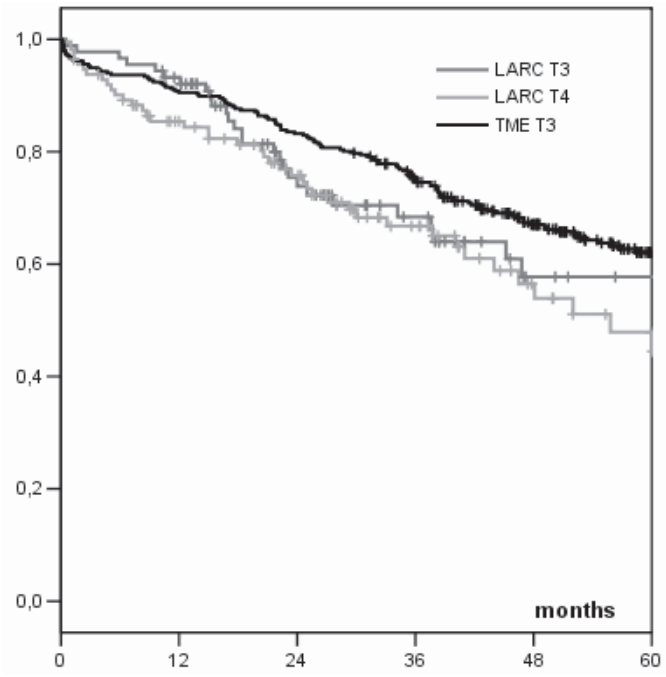

fig. 1	0	12	24	36	48	60	months
TME T3	316	288	264	232	166	98	at risk
	100	91	84	76	67	62	% surv
LARC T3	89	81	48	32	16	13	at risk
	100	93	75	68	58	58	% surv
LARCT4	112	86	67	43	22	15	at risk
	100	85	76	67	56	48	% surv
						p=0,630	log rank

Figure 1. Kaplan-Meier: Overall survival for the different patient populations.
No difference is observed between T3 and T4 LARC tumours. TME treated patients show the same survival as LARC patients (p = 0.630)

DISCUSSION

We demonstrated that in a group of locally advanced rectal carcinomas with a poor pre-treatment prognosis the majority of cases will end up with a prognosis comparable to mobile T3 tumours. The applied multimodality treatment resulted in a relatively low percentage of CRM positive cases (17%). Survival rate in CRM negative LARC tumours are similar to the results in TME treated mobile rectal tumours after preoperative radiotherapy.

In recent years the treatment of mobile, or primary resectable, rectal cancer has improved dramatically. The hypothesis that the introduction of TME surgery would result in an improvement of overall survival (13) in addition to improved local control, was confirmed in the Dutch

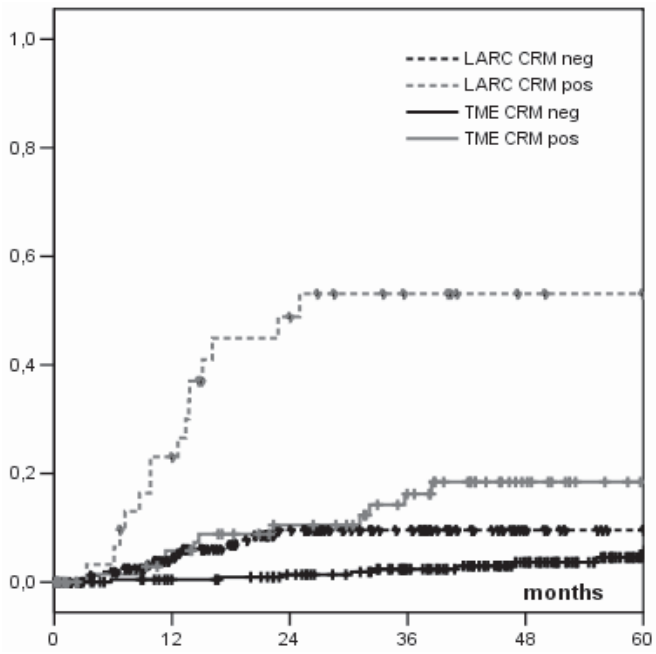

fig. 2	0	12	24	36	48	60	months
TME	238	220	208	184	140	81	at risk
CRM neg	0	0	1	2	4	5	% LR
TME	78	64	53	43	24	14	at risk
CRM pos	0	6	10	14	18	18	% LR
LARC	167	135	91	65	36	26	at risk
CRM neg	0	4	10	10	10	10	% LR
LARC	34	23	13	8	3	2	at risk
CRM pos	0	23	49	53	53	53	% LR
						p=0,000	log rank

Figure 2. Kaplan-Meier: Local recurrence in both patient population in relation to circumferential margin involvement

TME trial (12). Local control was further improved by the introduction of 5 times 5 Gy preoperative radiotherapy. This combination resulted in very low local recurrence rates; in fact, local recurrence does not contribute significantly to mortality anymore. From subgroup analyses it became clear that prognosis of patients with an involved CRM is significantly worse (14). Locally advanced patients are by definition patients with a visceral mesorectal fascia exposed to the threat of tumour involvement. TME surgery in those patients, even after short course of preoperative irradiation, will inevitably lead to a high percentage of irradical resections and

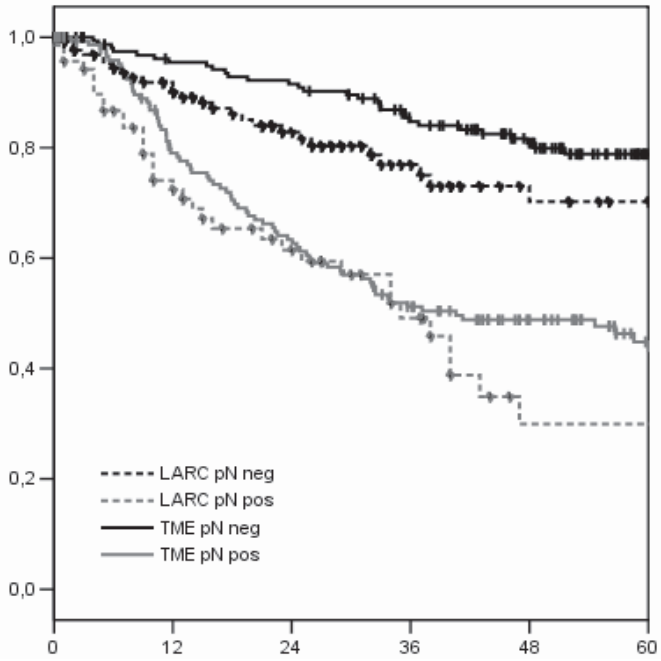

fig. 3	0	12	24	36	48	60	months
TME	166	147	141	120	95	54	at risk
pN neg	100	96	92	85	82	79	%meta
TME	150	115	90	71	52	30	at risk
pN pos	100	81	64	52	49	45	%meta
LARC	132	103	68	41	26	20	at risk
pN neg	100	92	83	77	73	70	%meta
LARC	69	45	31	18	6	6	at risk
pN pos	100	74	61	49	30	30	%meta
						P=0,0000	log rank

Figure 3. Kaplan-Meier: Metastatic free survival in both patient populations, in relation to lymph node status

subsequent higher local recurrence rate (12, 15). In this study a multimodality treatment for patients with locally advanced rectal cancer was benchmarked against a comparable group of patients from the TME study. The only difference was the initial estimation of the circumferential margin.One of the primary questions of the current study was, whether the use of multimodality treatment could reduce the number of irradical resections and subsequently contribute to an improved outcome.In both groups circumferential margin involvement is an important predictor of local recurrence. Long course preoperative radiotherapy effectively lowers the rate of positive surgical margins. In fact, in these patients the *a priori* high risk on a

Table 2. Cox regression Multivariate analysis

	Overall survival			**Local recurrence**			**Distant metastasis**		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
CRM neg	1			1			1		
CRM pos	2.13	1.54-2.93	0.000[#]	4.50	2.41-8.41	0.000[#]	2.39	1.71-3.34	0.000[#]
LAR	1			1			1		
APR	1.01	0.74-1.38	0.935	1.35	0.72-2.52	0.346	1.08	0.77-1.50	0.671
pN neg	1			1			1		
pN pos	1.93	1.44-2.59	0.000[#]	2.48	1.32-4.66	0.005[#]	3.10	2.23-4.32	0.000[#]
TME	1			1			1		
LARC	1.50	1.09-2.06	0.013[#]	3.75	2.00-7.02	0.000[#]	1.49	1.06-2.09	0.020[#]

CRM: circumferential resection margin, LAR: low anterior resection, APR: abdomino-perineal resection, pN: pathological lymph node status, HR: hazard ratio, 95% CI: 95% confidential interval, [#] significant (p< 0.05)

Table 3. Hazard ratio Circumferential resection margin and lymph node status combined

	TME group				**LARC group**			
	CRM neg		**CRM pos**		**CRM neg**		**CRM pos**	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Overall survival								
pN neg	1		0.98	0.46-2.09	1		2.94 [##]	1.37-6.30
pN pos	1.41	0.91-2.18	4.40 [##]	2.80-6.89	2.06 [#]	1.19-3.56	3.95 [##]	2.00-7.83
Local recurrence								
pN neg	1		0.00 [*]		1		5.23 [##]	1.71-16.01
pN pos	1.16	0.31-4.32	10.52 [##]	3.60-10.75	1.49	0.49-4.55	11.20 [##]	4.40-28.48
Distant metastasis								
pN neg	1		1.26	0.518	1		2.19	0.82-5.83
pN pos	2.44 [##]	1.48-4.03	8.64 [##]	5.18-14.44	2.71 [##]	1.49-4.94	4.20 [##]	1.97-8.95

CRM: circumferential resection margin, pN: pathological lymph node status, HR: hazard ratio, 95% CI: 95% confidential interval, [#] p<0.05, [##] p<0.01, [*] no events (n=30)

positive CRM was lowered to a level significantly lower than in TME patients (17% versus 25%). The importance of a negative surgical margin is highlighted by the finding that prognosis for survival is equal to TME patients with negative margins.

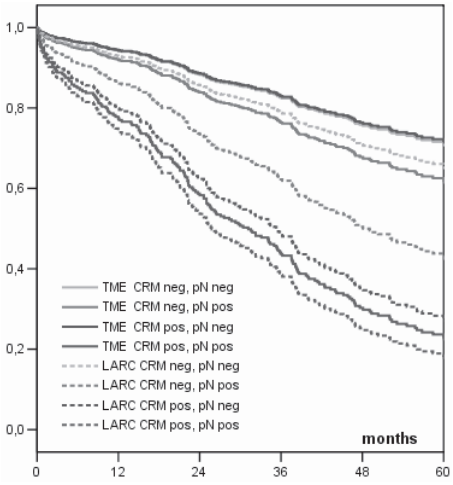

Figure 4a. Cox regression: overall survival, categorized in treatment, margin and lymphnodes

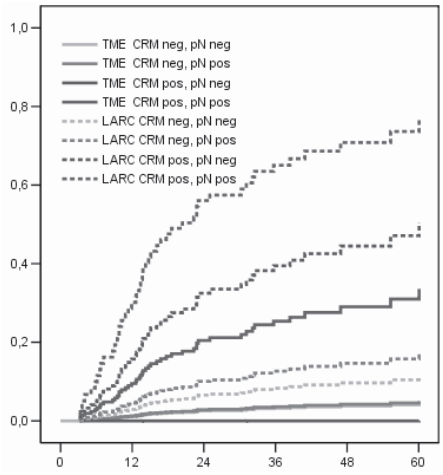

Figure 4b. Cox regression: local recurrence, categorized in treatment, margin and lymphnodes

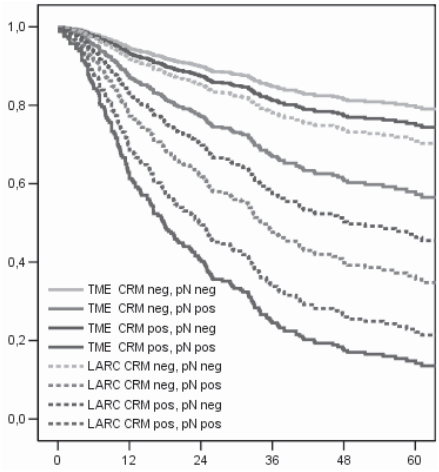

Figure 4c. Cox regression: metastatic free survival, categorized in treatment, margin and lymph nodes

Nodal status in TME and LARC patients are different entities. Whereas in TME patients the initial nodal status is recognised, in LARC patients an unknown number will have had positive nodes that have been sterilized due to the neoadjuvant therapy. In this case, pN0 consists of an heterogeneous group of patients who were initially node negative and patients whose metastatic tumours responded well to treatment. In all patients, node positivity was associated with a higher local recurrence risk. However, node positive LARC patients had a significantly higher risk than their TME counterparts. This might be explained by the presence of non-responders in the node positive LARC group. These patients have a worse prognosis due to the therapy-resistance in addition to their lymph node status. Another possible explanation for the higher risk of local recurrence in more advanced stages of nodal involvement was

published by Steup and Fujita (16, 17). They demonstrated a positive correlation between nodal stage and lateral nodal involvement. A higher local recurrence rate in node positive LARC patients, especially in the midrectal segment, where most of the lateral nodes reside in the obturator fossa, suggest a higher nodal stage contributing to the development of local recurrence originating in this lateral nodal depot. Indirectly, the absence of this phenomenon in low rectal cancer may support the theory that low tumours do not drain preferably in the lateral lymph nodes. The differences between lymph node positive LARC and TME patients with respect to the development of local recurrence reflects the higher stage of the LARC patients.

Another interesting point is the prognostic value of CRM involvement in node negative T3 patients. In the patients treated with short-term radiotherapy (TME group), no local recurrence occurred during follow up, whereas LARC patients have a high chance on local recurrence (HR 5.23, p<0,00001). This suggests that 5 x 5 Gy effectively prevents local recurrences in positive margin patients without nodal disease, but not in CRM+ patients with nodal metastases. This conclusion is supported by the fact that in the control arm of the TME study without 5x5 Gy preoperative irradiation local recurrence rate equal was in node negative and node positive patients. In addition, it underlines that LARC patients who still have a positive CRM after chemoradiation are poor responders and have a very poor prognosis.

Above mentioned demonstrates that both circumferential margin and nodal status play an important role in the local control after rectal cancer surgery. With this regard, mobile and advanced rectal cancers obey to the same rules. Success of multimodality treatment for advanced rectal cancer depends on how well these primary unfavourable variables are controlled. Our results demonstrate that outcome for a LARC patient is similar to TME patients when these unfavourable parameters have been controlled by chemoradiation. The key role in recent progress in the treatment of locally advanced rectal cancer is the cooperation between the different modalities. Several multimodality strategies have been developed and evaluated. Due to lack of randomised trials, there are still controversies in what treatment and especially which sequence offers the best survival. However, some agreement seems to be present: at this moment long-term radiotherapy (50 Gy) with concomitant fluoroucil (5-FU) based chemotherapy is becoming the most used neoadjuvant therapy (18-20).

Last years preoperative combined adjuvant therapy has gained acceptance as standard therapy in favour of postoperative regimens (21-24). Key factor in this development is the improved possibility of preoperative imaging and thus staging (25, 26).

CONCLUSION

Insight into the tumour biology of progressing rectal cancer has been gained by the comparison of the response to two different treatment strategies. The interaction between two

independent variables i.e. positive circumferential surgical margin and positive lymph nodes and its relevance for the development of local recurrence is obvious. Another observation was, that local recurrences, at least partly could be explained as metastatic disease in the lateral lymph node compartment. The question that remains to be answered is whether further intensification of neoadjuvant local or more attention to systemic treatment will help to control this type of recurrence. Especially in low rectal cancer, 5x5 Gy preoperative irradiation followed by immediate surgery cannot prevent a relatively high positive circumferential margin rate (27). In more advanced T3 and T4 cases long course neoadjuvant treatment (LCNT) effectively reduces the number of positive margins, and therefore LCNT may also play an important role in T3 low rectal cancer. Selection for either treatment requires high-resolution preoperative imaging. Overall LCNT is able to restrain progressing rectal cancer. In the future, the isolated local recurrence without the development of distant metastatic disease will be very rare. Most patients will develop distant metastatic disease and one out of three will die of metastatic disease. The focus of upcoming studies also will have to include proper patient selection for adjuvant treatment.

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10

Minimal residual disease assessment in sentinel nodes of breast and gastrointestinal cancer: a plea for standardization

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SUMMARY

Lymph node dissection plays an important role in staging and treatment of cancer patients with solid tumors. Sentinel node biopsy (SNB) has been introduced to minimize the extent of surgery and to enable minimal residual disease (MRD) assessment without compromising accurate staging and survival. This review addresses the variation in technical aspects and outcome of SNB and MRD assessment in patients with breast and gastrointestinal cancer. There is a need for quality control leading to standardization of SNB and consecutive pathological examination to enable reliable comparison of studies, leading to consensus of diagnostic and therapeutic strategies.

INTRODUCTION

The histological status of lymph nodes is one of the most important prognostic indicators in patients with cancer originating from solid tumors. Staging patients to determine the need for adjuvant therapy presently occurs through lymphadenectomy. Apart from lymphadenectomy as a staging tool, it may also serve a therapeutic aspect, even in patients without nodal involvement[1,2]. Overall survival of colorectal cancer patients without nodal involvement, improves with increasing number of lymph nodes recovered[3]. Also in invasive bladder cancer, both node-negative and node-positive patients had prolonged overall survival with an increasing number of lymph nodes examined[4]. This benefit is possibly due to the presence of MRD in H&E-negative lymph nodes.

Lymphadenectomy may be associated with considerable morbidity, especially in breast cancer and melanoma patients. To minimize the extent of lymphadenectomy without compromising accurate staging and survival, SNB has been introduced. Sentinel nodes are known as the first possible sites of metastasis along the route of lymphatic drainage from a primary tumor. The histopathological state of the sentinel node is presumed to reflect that of all regional lymph nodes. SNB can be performed by injecting either a vital dye, a radioactive colloid or both around the primary tumor. Techniques vary, however, substantially between institutions and researchers, which complicates reliable assessment of the role of SNB.

An amenity of the SNB is the lower number of lymph nodes that have to be examined compared to regional lymph node dissection. Laborious and expensive focused examination techniques like immunohistochemistry (IHC) and reverse transcriptase polymerase chain reaction (RT-PCR) can therefore be applied in a limited number of sentinel nodes to detect the presence of so-called minimal residual disease, also known as micrometastases. Micrometastases are defined as a cohesive cluster of malignant cells, greater than 0.2 mm and up to 2.0 mm in diameter, that are usually not detected with conventional pathological examination techniques. The prognostic significance of micrometastases and the therapeutical consequences of upstaging by MRD assessment, however, are far from clear yet. Nevertheless, in some countries treatment decisions are already based on MRD assessment, implying possible over treatment. This review addresses the role of SNB and MRD in (sentinel) lymph nodes in breast, gastric and colorectal carcinoma and pleads for standardized and randomized trials in this field.

BREAST CANCER

Axillary lymph node dissection (ALND) contributes to both treatment and staging. Overgaard reported large differences in local recurrence rates in a trial investigating the efficacy of radiotherapy following total mastectomy[5]. There were clear variations in the extent and

Table 1. An overview of the SNB studies in breast cancer

Reference	Type of tracer	Average no of SNs	Succesrate mapping (%)	Upstaging method	False-negative rate (%)
Nwariaku et al[36]	Tc + blue dye	1.84	81	s.s.	4
Borgstein et al[37]	Tc	1.2	100	IHC	2
Krag et al[38]	Tc	2.6	91	-	11
Hill et al[39]	Tc + blue dye	2.1	100	IHC	11
Veronesi et al[40]	Tc + blue dye	1.4	99	s.s.	7
Winchester et al[41]	Tc	3.1	90	s.s.	8
Bass et al[42]	Tc + blue dye	2.0	93	IHC	2
Morrow et al[43]	Tc + blue dye	1.8	79	-	13
Fraile et al[44]	Tc	2.0	96	IHC	4
Kollias et al[45]	Tc + blue dye	1.4	81	IHC	6
Tafra et al[46]	Tc + blue dye	2.2	87	IHC	13
Nano et al[47]	Tc + blue dye	-	87	IHC	7

Tc = 99m Technetium; s.s. = serial sectioning; IHC = immunohistochemistry

quality of surgery since more than half of the local recurrences appeared on the chest wall. It was concluded that radiotherapy improved local control with the current surgery. However, if surgical procedures would improve, the benefits of standard application of radiotherapy might be questionable. It is clear that the quality of surgery dictates the value of adjuvant treatment. This stresses the need for standardized and quality-controlled SNB as staging and treatment decisions depend on removing and investigating only one or a few sentinel nodes. Currently, most centres agree on using the combination of a radioactive tracer and blue dye, which improves the identification of multiple sentinel lymph nodes compared to the use of one tracer alone[6]. Table 1 highlights studies published since 1998 on SNB in breast cancer patients, with more than 100 patients included. Most centres use the combination of blue dye and radioactive colloid to detect sentinel nodes. In the displayed studies considerable variation exists in the volume of tracer used and the technique of examination of the resected sentinel nodes, which might lead to different success and false negative rates. The site of injection is often inaccurately reported and it remains unclear whether massage has been performed.

In focused examination studies of H&E negative lymph nodes, there is considerable variation in the applied technique, marker or antibody used and data analysis. Dowlatshahi showed upstaging by serial sectioning and immunohistochemistry of 9 to 33%[7,8]. The clinical relevance of MRD assessment is debatable. Studies that showed survival disadvantage due

to the presence of micrometastases included larger patient populations (range 147-921) and had more prolonged follow-up (at least 6 years) than studies that did not prove any survival difference. Moreover, most studies did not take the size of the micrometastases into account, whereas data already exist that the size of nodal metastases linearly correlates with survival[8]. Also the role of isolated tumor cells in lymph nodes has not been elucidated yet[9]. It might be difficult to distinguish isolated tumor cells from mesenchymal cells, mesothelial cells, transfer (contamination) artefact, and transport of benign or malignant epithelium. Many investigators probably often encounter these technical difficulties, but reports on these issues are remarkably scarce.

MRD assessment in sentinel nodes with immunohistochemistry and serial sectioning reveals a higher detection rate of micrometastases in sentinel nodes than in the regional lymph nodes[10]. This is in line with the sentinel node hypothesis. An overview study showed that in 38-67% of patients with breast cancer the sentinel node is the only involved lymph node[11]. When the sentinel node is the only involved lymph node it can be argued that ALND is not necessary. In the AMAROS trial (After Mapping of the Axilla Radiotherapy Or Surgery), coordinated by the European Organization for Research and Treatment of Cancer, patients with positive sentinel nodes are randomized to ALND or axillary radiotherapy. The presence of any tumour deposit, detected with either HE staining or IHC, has consequences for the local treatment of the axilla (i.e. surgery or radiotherapy) but not for systemic treatment. Recently, concern has been expressed that many pathology laboratories have adopted IHC techniques and many oncologists recommend adjuvant chemotherapy upon IHC detected metastases only[12]. Giving patients a toxic and often expensive treatment with possibly limited benefits, based upon IHC findings alone, is not backed up by the literature and should therefore not be encouraged.

It can be concluded for breast cancer patients, that the SNB is presently performed with acceptable success rates and low false negative rates despite considerable variation in SNB techniques. Special techniques to detect micometastases can lead to upstaging in a considerable number of patients, but it remains unclear whether these findings should affect the choice of adjuvant treatment.

GASTRIC CANCER

The widespread use of gastroscopy has led to increasing chance of identifying gastric cancer at an early stage. Nodal involvement occurs only in 2 to 18% in T1 tumors and in about 50% in T2 tumors[13]. This means that a larger than necessary lymphadenectomy is performed in a substantial number of patients. The debate on the benefits of D1 compared to D2 lymph node dissection is still ongoing. Also, the value of adjuvant therapy in relation to the extent of surgery is intensely discussed[14]. An extended lymphadenectomy is associated with considerable postoperative morbidity and mortality, especially in western countries[15,16]. However, reliable

tools are lacking to predict nodal involvement. SNB and its investigation might however gain a role in minimizing the surgical procedure and predicting the status of non-sentinel nodes. The studies on feasibility of SNB in gastric cancer are rather limited. Table 2 shows that different types of tracers are being used and a ranging number of SNs are retrieved. Moreover, only in one SNB study upstaging techniques were applied[17]. Endoscopic submucosal injection has shown to be a feasible route of administration of a radioactive tracer or a dye. Identification of the sentinel node using a radiolabelled colloid and perioperative detection with a gamma-ray detection probe has the drawback of detecting not only radiation from lymph nodes, but also from the adjacent injection site. Therefore, most experience has been gained so far with the application of dyes. All the displayed studies, initiated in the Far East, showed acceptable feasibility in early stage disease (i.e. T1 or T2). In Western countries however, gastric cancer is often diagnosed at an advanced stage, which questions the role of SNB in these patients.

Table 3 displays that two out of five IHC studies, using anticytokeratin antibodies showed an adverse effect of the presence of micrometastases. Remarkable are the differences in

Table 2. An overview of the SNB studies in gastric cancer

Reference	No of pts	Type of tracer	Volume of tracer (ml)	Average no of SNs (range)	Succesrate mapping (%)	False-negative rate (%)
Hiratsuka et al[48]	72	Indocyanine green	5	2.6 (1-9)	99	10
Aikou et al[17]	18	Tc + blue dye	2 (Tc)	3	94	17
Yasuda et al[49]	26	Tc	2	4 (2-8)	100	18
Ichikura et al[50]	62	Indocyanine green	4 or 8	4.5 (1-12) resp. 8.6 (1-25)	100	13
Kitagawa et al[51]	145	Tc	2.0	3.6 (1-8)	95	8
Miwa et al[52]	211	Blue dye	0.8	6 (1-19)	96	11

Tc = 99m Technetium

Table 3. Immunohistochemistry studies on H&E-negative lymph nodes in gastric cancer

Reference	Antibody	No of H&E-node-negative patients	No of nodes per patient	Node sectioning	Upstaging (%)	Prognostic value
Maehara et al[53]	CAM 5.2	34	12.4	single	23.5	adverse
Cai et al[54]	CAM 5.2	69	24.6	single	25	controversial
Morgagni et al[55]	MNF 116	139	10.7	multi	17	no difference
Fukagawa et al[56]	AE1/AE3	107	41.9	single	35.5	no difference
Lee et al[57]	AE1/AE3	70	23.7	single	40	adverse

antibodies used, the number of resected lymph nodes and proportion of patients upstaged. Noguchi et al used RT-PCR with keratin 19 as a marker to detect micrometastases and found that this was a more sensitive method than histological examination for the detection of gastric micrometastases in lymph nodes[18]. The prognostic significance of micrometastases, detected with this technique, was however not addressed.

The majority of the reports on gastric carcinoma originate from specialized centers that have been able to gain experience with the technical demanding procedure in a patient population less prone to postoperative morbidity and mortality than in Europe and the USA.

In conclusion, the initial and limited experience in SNB has a potential value in staging and treating gastric cancer patients. However, only patients with early stage disease, a patient category not very often encountered in Western population, may benefit from SNB. Moreover, the existing variation in technical aspects of SNB and MRD assessment hampers the introduction of treatment decisions based on MRD assessment.

COLORECTAL CANCER

The treatment of node-negative colorectal cancer consists of surgical resection of the primary tumor without adjuvant therapy. However, up to 30% of these patients will develop metastases possibly due to micrometastases in the regional lymph nodes. We showed that patients with CEA RT-PCR negative lymph nodes had a significantly better five-year disease-free survival than patients with positive lymph nodes (91 versus 50%, p=0.02)[19]. Three other RT-PCR studies[20-22] also showed an adverse effect on the prognosis whereas only three of ten immunohistochemistry studies showed an adverse effect[22,23]. Again, the IHC studies show clear variation in the number of resected lymph nodes, the use of serial sectioning and antibodies, and the degree of upstaging, which ranges from 10 to 76%[22,24-32]. Noura et al studied the same paraffin-embedded lymph nodes with CEA RT-PCR and cytokeratin immunohistochemistry and showed that CEA RT-PCR had prognostic value whereas immunohistochemistry did not[22].

SNB in colorectal cancer patients is still in childhood. In contrast to breast cancer patients, SNB in colorectal cancer is not performed to avoid unnecessary lymphadenectomy but to enable focused examination of few lymph nodes. An important consequence of intraoperative SNB in colorectal cancer patients is the identification of aberrant lymphatic drainage patterns occurring in up to 14% of the patients leading to an adjustment of the initial surgical resection plan[33,34]. Table 4 summarizes SNB studies on colorectal cancer patients, with more than 25 patients included. Blue dye is used in most of the studies with moderate variation in volume and site of injection. However, the number of detected SNs ranges widely. Success rates, false-negative rates and upstaging techniques vary and are influenced by disease

Table 4. An overview of the SNB studies in colorectal cancer

References	No of patients	Identification time (min)	Success rate (%)	Average no of SLNs (range)	Upstaging methods	False-negative rate (%)
Joosten et al[58]	50	15	70	3	IHC	60
Wiese et al[59]	83	5-10	99	1.9	s.s. and IHC	9
Feig et al[60]	48	-	98	2.6	IHC	38
Wong et al[61]	26	2-5	92	2.8	s.s. and IHC	6
Saha et al[62]	203	1-5	98	(1-4)	s.s. and IHC	6
Merrie et al[63]	26	20*; 26 – 106**	88	3 (0-8)	RT-PCR	45
Esser et al.[64]	31	-	58	-	-	33
Broderick-Villa et al[65]	51	-	92	1.5	IHC	50
Wood et al[66]; Bilchik et al[67]	100	-	97	2	s.s. and IHC	11
Fitzgerald et al[68]	26	5-10	88	2.5	s.s. and IHC	40
Paramo et al[69]	55	5	82	1.9	s.s. and IHC	7
Kitagawa et al[35]	56	120	91	3.5	-	18

stage. In rectal cancer, the dye method has its limitations because of the restricted visibility of the transit of dye into the SNs[35].

In summary, SNB in colorectal cancer patients is a technical demanding procedure with variable success rates. Although MRD assessment can lead to profound upstaging, there is no clear evidence yet that it should affect adjuvant treatment decisions. Still, in some countries colorectal cancer patients with sentinel node micrometastases are already receiving systemic adjuvant therapy. SNB and MRD assessment techniques are currently being optimised, which may lead to more tailored adjuvant treatment, based upon MRD assessment.

CONCLUSION

Limiting the extent of surgery in the treatment of solid tumors through SNB is technically feasible. However, when comparing studies investigating the role of SNB, there is a large variation in patient selection, and type and volume and location of tracers injected around the tumor. This variety complicates trial comparison, which hampers application of SNB into daily practise. Minimal residual disease assessment by serial sectioning, immunohistochemistry and RT-PCR is possible and may lead to considerable upstaging. The results from studies

addressing the prognostic role of micrometastases are often contradictory, which might be due to the use of different examination techniques, markers, antibodies and differences in sample size and length of follow-up. This variation in techniques of SNB and MRD assessment precludes the availability of evidence-based diagnostic and therapeutical guidelines in the near future. Quality control leading to standardization of SNB and MRD assessment is necessary to enable reliable comparison of different studies. In this way only, we can determine the prognostic role of MRD and develop tailored adjuvant treatment, based upon MRD assessment of lymph nodes retrieved after limited surgery.

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11 General discussion and summary

GENERAL DISCUSSION

Gastric cancer

In 2002, 933,900 cases of gastric cancer were diagnosed world wide (http://info.cancerresearchuk.org/cancerstats/). Gastric cancer ranks second after lung cancer when it comes to cancer mortality: there are 700,300 gastric cancer deaths per year. Treatment is based on surgical resection of the tumour. In case of localised disease, surgical resection offers favourable survival rates. The problem is however that localised disease is rare in Western countries: only in case of advanced stage, signs and symptoms may indicate the likelihood of gastric cancer. Furthermore, mass screening programs that are helpful in diagnosing early stage are successfully employed in Japan, but are not common in Europe or the United States.

Surgery

Apart from stage disease, the quality and extent of surgery is a prognostic factor as well. In Japan (as much as 19% of all malignancies are gastric cancers), surgery does not only involve tumour resection. Extended lymph node dissection is performed on a routine basis as well. The extent of lymphadenectomy focuses on the main question: are the lymph nodes the tumour is draining to merely *indicators* or also *governors* of disease? In other words: does lymphadenectomy only serve staging purposes (opinion in Western countries) or has it also a therapeutical goal (reducing the likelihood of distant spread, [1-4]opinion in the Eastern Asia)? To answer this question, several randomised trials have been performed. Remarkably, in Japan no prospective randomised trial was ever performed to substantiate their own practise: convinced of the benefits of D2 dissection, setting up such trial has always been considered unethical by both patients and doctors. The two large European trials with adequate design, power and execution, were the British MRC[5,6] and the Dutch Gastric Cancer D1D2 trial[4,7,8]. Both trials failed to show any benefit from extended surgery. In the editorial accompanying Henk Hartgrink's final report on the Dutch D1D2 trial, Petrelli[9] concluded that the debate on the benefits of D2 dissection is over: there is no survival benefit of extended surgery after a median follow-up 11 years, and therefore no reason perform this kind of surgery on Western gastric cancer patients ("it's time to move on"). However, Petrelli's conclusion might be premature: postoperative morbidity and mortality of D2 dissection was considerable in both European trials and might have obscured a survival benefit of extended surgery. Indeed, subgroup analyses from the D1D2 trial show improved survival in patients who were assigned to D2 dissection and did not undergo organ resection. (During trial accrual, resection of spleen and pancreatic tail was not only preformed in case of organ involvement. It was also performed assuming that organ resection was necessary in order to achieve adequate nodal clearance (stations 10 and 11) in case of proximal gastric cancer). More recent reports show that organ preservation techniques can safely performed in Western patients, with low morbidity and mortality without compromising the extent of lymph node dissection.[10-14] Moreover, recently

the first prospective randomised trial was published showing a survival benefit of extended lymph node dissection: patients undergoing D3 gastrectomy had better 5 year overall survival rates than patients who were treated with D1 dissection. (59.5% vs. 53.6%, P = 0.041).[15] These interesting results were obtained in a single-center study, indicating that high-volume surgery in experienced centers might be an explanatory factor. Moreover, there is another subset of patients that benefit from D2 dissection: subgroup analyses from the D1D2 trial indicate a trend for better survival in N2 patients after a D2 dissection (lymph nodes are probably not only indicators but also governors of disease). It is likely that performing a D1 dissection without splenectomy and resection of the pancreatic tail, together with dissection of at least 15 nodes (a so-called over D1 (D1+) resection) results in better outcome.[16]

Another way of reducing overall morbidity and mortality is to tailor surgery to the individual gastric cancer patient. It is known from the D1D2 trial that patients older than 70 years of age, subjected to D2 dissection are more likely to suffer from postoperative complications.[4] Performing this kind of extended surgery in the elderly seems inadvisable.

A final and promising way of tailoring surgery involves resecting only those lymph nodes that are most likely to be involved by tumour. Prediction of nodal involvement by preoperative imaging has limited value. The concept of the Maruyama Index of Unresected Disease[17,18] (MI, see Chapter 3) may offer new opportunities: by collecting individualised patient and tumour characteristics prior surgery, the chance of nodal involvement of the D1 and D2 stations can be predicted by comparing these individual data to a large database of close to 4,000 Japanese gastric cancer patients. In this manner, unnecessary lymphadenectomy of uninvolved lymph nodes is prevented, thus reducing the likelihood of postoperative complications. The value of the MI has been established retrospectively in both the US Intergroup trial 0116[19] and the Dutch Gastric Cancer trial[18]: performing individualised "low-Maruyama-index-surgery" is probably better than dissecting the complete N2 echelon in every gastric cancer patient; postoperative complications are reduced and long term survival improves. Of course, it is premature to introduce the Maruyama concept before testing it in a prospective fashion. The newly designed CRITICS study (see later) offers the opportunity.

(Neo-)adjuvant treatment

Because the results of surgery alone are poor in case of locally advanced disease (i.e. extension through the gastric wall and involvement of peri-gastric nodes), attempts have been made to improve treatment outcome applying adjunctive treatment regimens. In contrast to colon cancer, adjuvant chemotherapy has not shown to be effective.[20-23] The addition of radiotherapy however (external-beam radiation delivered to the site of surgery and its draining lymph nodes) to fluorouracil and leucovorin after surgery is beneficial: the US SWOG trial showed that patients after multi-modality treatment had better median survival than patients treated with surgery alone (36 vs. 27 months, P = 0.005).[24] Also disease-free survival was superior (30 vs. 19 months, P<0.001). This trial was criticised on some points however,

the most important one being the fact that the majority of the patients (54%) had not even undergone a resection of the peri-gastric nodes (D1 level). The important confounding role of surgery was stressed earlier, and keeping this in mind, the question whether postoperative chemoradiation is of any value after optimal surgery remains largely unanswered. There are however some reports from non-randomised studies that adjuvant chemoradiotherapy in D2-resected gastric-cancer patients is tolerable[25] and can prolong survival and decrease recurrence.[26]

Another way of adjuvant treatment concerns peri-operative treatment. Theoretical advantages of preoperative treatment include increasing the chances for curative resection and relief from tumour–related symptoms, both through the mechanism of downstaging. Moreover, tumour response to chemotherapy can be determined. The British MRC trial tested in a prospective randomised trial whether peri-operative epirubicin, cisplatin and infused fluorouracil (ECF) could improve overall survival in patients with resectable adenocarcinoma of the stomach, esophagogastric junction, or lower esophagus.[27] Rates of postoperative complications did not differ between the perioperative-chemotherapy group and the surgery alone group (46 percent and 45 percent, respectively), neither did the numbers of deaths within 30 days after surgery. With a median follow-up of four years, the perioperative-chemotherapy group had a higher likelihood of overall survival (hazard ratio for death, 0.75; P=0.009; five-year survival rate, 36 percent vs. 23 percent). Interestingly, the resected tumors were significantly smaller (median size 3 cm vs. 5 cm, P<0.001) and less advanced in the perioperative-chemotherapy group (proportion T1/T2 tumours 52% vs. 37%, P = 0.002, proportion N0/N1 disease 84% vs. 71%, P = 0.01). These findings favour preoperative treatment considering the difficulty to achieve curative resection in case of locally advanced disease (a patient category often encountered in Western countries). A disadvantage of infusional fluorouracil however, is the implantation of central venous catheter devices and the use of portable infusion pumps that bare the risk of complications such as thrombosis and wound infection. An alternative might be capecitabine, a prodrug and oral analogue of 5-FU that is believed to mimic continuous infusion of 5-FU. Capecitabine has demonstrated to be equally effective in tumor control and to be less toxic than intravenous 5-FU in patients with stage III and IV colon cancer.[28-30]

Data from the well designed MAGIC and SWOG/Intergroup studies raise the important question whether postoperative chemoradiotherapy improves survival and/or locoregional control in patients that receive neoadjuvant chemotherapy followed by a D1+ gastric resection. The recently developed CRITICS trial (ChemoRadiotherapy after Induction chemoTherapy In Cancer of the Stomach, leading group Dutch Colorectal Cancer Group) randomises gastric cancer patients between 2 arms: ***1***. 3 courses of ECC chemotherapy prior to D1+ surgery followed by 3 additional ECC courses or ***2***. 3 courses of ECC chemotherapy prior to D1+ surgery followed chemoradiotherapy (45 Gy in 25 fractions plus capecitabin and cisplatin). Primary endpoint is overall survival. The trial is to be launched in 2007.

A final comment needs to be made on the role of sentinel node biopsy (SNB) and the clinical relevance of minimal residual disease (MRD) in gastric cancer patients. SNB, a concept pioneered by Morton et al.[31] in melanoma patients, has gained wide acceptance in the treatment of breast cancer patients: analysis of the sentinel node is used to predict the presence of metastasis in the corresponding nodal basin. In this manner, morbidity of unnecessary lymph node dissection is reduced without compromising locoregional control. To avoid inaccurate mapping, SNB should only be performed in early gastric cancer lesions: distortion of lymphatic pathways in locally advanced disease hinders reliable mapping. Japanese data show encouraging data, although the rate of accurate detection might be low for large tumours.[32,33] The fact that results in Western patients are less favourable is probably due to the more advanced stages of disease diagnosed in the West.

As mentioned before, disease recurrence is a major problem in gastric cancer patients. The current method for staging in gastric cancer is insufficient: not only are often too few lymph nodes removed leading to systematic understaging, also routine investigation of the removed nodes applying hematoxylin and eosin staining may not be accurate enough. To illustrate this inaccuracy, even after a complete tumor resection many patients who are considered to be node-negative suffer from disease recurrence. Searching for occult tumour cells (OTC) in these lymph nodes may identify this high-risk subset of patients. OTC comprise micrometastases with its size being more than 0.2 mm but less than 2.0 mm, and isolated tumor cells (size less than 0.2 mm). A recent case-control study by Doekhie et al.[34] showed that, although identification of OTC is technically possible, it can not predict disease recurrence. This is line with Japanese data that showed that the presence of immunohistochemically detected micrometastases in the regional lymph nodes did not affect the survival of pT2N0M0 gastric cancer patients who had undergone gastrectomy with D2 lymph node dissection.[35] The number of lymph nodes removed may serve as a more reliable predictor, stressing again that lymph node dissection has therapeutical value.[36]

RECTAL CANCER

In 2002, 1,023,200 patients were diagnosed with colorectal cancer worldwide (http://info.cancerresearchuk.org/cancerstats/). In Europe 11% of all cancer cases were bowel malignancies. It is the fourth most common cause of death from cancer worldwide accounting for 8% of all deaths from cancer. There have been steady increases worldwide in the numbers of people being diagnosed with bowel cancer over the last 25 years. Approximately one third of the colorectal cancers are rectal cancers.

As for gastric cancer, local recurrence is important issue for concern. Again, well-performed surgery is an important prognostic variable. It is increasingly acknowledged that local failure is more a matter of surgical technique rather than of aggressive biological tumour behavior.

Incomplete tumour resection with involvement of the circumferential resection margin by tumour and/or lymph nodes is the most important risk factor for local recurrence. The importance of complete resection is stressed by the fact that postoperative radiotherapy is not effective in case of irradical resection and therefore does not compensate for low-quality surgery.[37] This emphasizes the need for precise staging during the initial work-up for each rectal cancer patient. By accurate MR imaging, tumours can be classified according to the risk or local recurrence. Involvement of the mesorectal fascia calls for prolonged irradiation prior to surgery, leading to downstaging and –sizing, facilitating curative (R0) resection.

The benefits of short term preoperative radiotherapy (5x5 Gy)

The Swedish rectal Cancer Trial showed that 5x5 Gy followed by conventional surgery of operable surgery increased both local control and overall survival[38], also in the long run at a median follow-up of 13 years.[39] The efficacy of this regimen in TME treated patients was unknown until the early data of the TME trial were released: at a median follow-up of 2 years, local recurrence rate was lower in irradiated patient (2.4% vs. 8.2%, P<0.001).[40] There was however no effect on overall survival, hypothetically due to the rather short period of follow-up. With a median follow up of 6 years, irradiated patients still have significant lower recurrence risk compared to non-irradiated patient. (5.6% vs. 10.9%, P<0.001), chapter 8). The benefits of preventing local failure need to be stressed: intractable pain, incontinence due to sphincter ingrowth and rectal blood loss are prevented in many rectal cancer patients. In this respect 5x5 Gy is a valuable regimen. Moreover, the short term adverse effects of this radiotherapy are only minor, although perineal wound dehiscence after irradiating the perineum is a matter of concern.[41] On the long run however, fecal incontinence occurs more often in irradiated patients: 62% vs. 38%, P < 0.001 (chapter 7).[42] Moreover, satisfaction with bowel function is significantly lower and the impact of bowel dysfunction on daily activities was greater in irradiated patients compared to patients who underwent TME alone. This should prompt the medical community to tailor radiotherapy to those patients that are most likely to benefit from it. Not every rectal cancer patients has equal benefit from radiotherapy: the efficacy depends partly on the height of the rectal tumour. Therefore, it is tempting to perform subgroup analyses from the TME trial on tumour height in order to narrow the indications for 5x5 Gy. Caution is warranted: statistical power is often insufficient to detect clinical relevant differences. Furthermore, daily practice tells us that it is difficult to determine exact tumour position prior to surgery: discrepancies between endoscopy findings, CT/MRI imaging and intra-operative findings are not uncommon. Nevertheless, one may wonder about the implications of these analyses for rectal cancer treatment. Subgroup analyses do provide a degree of evidence, especially when the analyses are derived from the largest study so far on TME treated patients. Local failure after treatment of proximal tumours is relatively rare, making the number of patients needed to irradiate in order to prevent one local recurrence substantial. Moreover, the difference in local recurrence rate between the two randomisation

arms is non-significant (3.7% vs. 6.2%, P=0.122). For low-lying rectal cancers there is neither any significant effect of radiotherapy (10.7% vs. 12.0%, P = 0.578). An import confounding factor in distal rectal cancers is the rate of CRM involvement. As it appears from the TME trial, APR patients have undergone more often irradical resection than patients treated with anterior resection (26.5% v 12.6%, P < .001). Also, survival is substantial lower (38.5% v 57.6%, P = .008).[43] This is in line with a retrospective series from Leeds involving 190 APR and 371 AR patients, local recurrence was higher in case of APR (22.3% versus 13.5%, P = 0.002), overall survival lower (52.3% vs. 65.8%, P = 0.003).[44] Even after introduction of TME the incidence of CRM involvement in the APR group (41%) was much higher than in the AR group (12%) (P = 0.006). Finally, the Norwegian Rectal Cancer Group stipulated the same problem: in their prospective observational cohort study involving 2,136 patients with rectal cancer within 12 cm of the anal verge, 10 percent local recurrence after anterior resection and 15 percent after abdominoperineal resection was seen (P=0.008).[45]

Future challenges in rectal cancer treatment

Establishing resection without involved margins

Preoperative imaging with the aim to distinct operable from locally advanced disease is crucial. MRI scanning is the only reliable tool to assess mesorectal fascia involvement and should be done in each rectal cancer patient.[46] Of course, scanning a patient is not enough, gaining the radiological expertise to interpret the images is important as well. In case of suspected mesorectal fascia involvement, 5x5 Gy is not a good option. Hypofractioned preoperative radiotherapy followed by immediate surgery does not lead to downsizing[47] and does therefore not facilitate complete resection. Prolonged irradiation (25x2Gy) followed by surgery carried out 4-8 weeks following the completion of radiotherapy, reduces tumour size and therefore increases the chances for radical resection. According to several phase II studies[48-50] the addition of continuous infusion fluorouracil (FU) chemotherapy to external-beam radiation therapy potentates this downsizing and –staging effect. The addition of oxaliplatin to intravenous continuous infusion FU and radiotherapy for patients with locally advanced rectal cancer may be associated with even a higher pathologic complete response rate[51] up to 25%, but is associated with more acute toxicity than when FU is used alone.[52] Apart from acute side effects, late morbidity should be a matter of concern as well. In chapter 7 we showed the detrimental long-term effect of 5x5 Gy on bowel function.[53] The impact of prolonged chemoradiation is probably substantial as well, but still needs to be clarified.

APR patients constitute a separate category of patients; in the TME trial CRM involvement was unacceptable high (26.5%) and tumour perforation occurred frequently (13.7%)[54] The difficulty to obtain margins in distal lesions is understandable: when the mesorectal plane is followed completely down onto the sphincter apparatus, the risk of involved margins increases as the mesorectum is a only a thin structure when it closes into the sphincters.

This "coning in" into the tumour is prevented when the perineal phase is commenced earlier during rectal cancer surgery: by performing a cylindrical resection with removing the levator muscles en bloc, the risk of inadvertent perforation due to excessive manipulation during the abdominal phase is reduced. This radical resection may lead to less margin involvement but leaves a substantial defect that calls for closure using for example myocutaneous flaps in order to facilitate wound healing.[55-58]

Minimising the morbidity from rectal cancer treatment

TME offers the opportunity to work under close vision of nerves that are important for bladder and sexual function. Yet, there is still room for further improvement considering the degree of dysfunction that many patients report, even if they did not undergo radiotherapy. Although rectal cancer surgery may inevitably cause a certain level of dysfunction, all efforts should be directed towards optimal identification and preservation of important nerve structures. This might imply further training of surgeons in order to obtain maximum exposure of the operative field. We have to keep in mind however that bowel, bladder and sexual dysfunction is partly physiological in the elderly and therefore cannot be ascribed solely to the detrimental effects of rectal cancer treatment.

In contrast to (neo-)adjuvant treatment surgery is the mainstay of cure of rectal cancer, making a certain level of side effects acceptable. Short term preoperative radiotherapy however is responsible for "only" a relatively small, but statistically significant reduction in local recurrence risk compared to surgery.(chapter 8) Considering the severe symptoms that accompany local failure the administration of preoperative radiotherapy seems justified. Moreover, it has to be stressed that local recurrence was chosen as primary endpoint of he TME trial, and not overall survival. The fact however, that there is hardly any effect of radiotherapy on overall survival at a median follow-up of 6 years (63.5% vs. 64.2%, P=0.260), raises the question whether every rectal cancer patient should be offered this toxic radiotherapy regimen. As we know from subgroup analyses from the TME trial, local recurrences are relatively rare when rectal cancer is located more than 10 centimeters from the anal verge. One could argue not to irradiate these patients, especially when it concerns (elderly) patients with already moderate bowel function prior to surgery: fecal incontinence is considerable in irradiated patients, even when it concerns proximal cancer. The impact of bowel dysfunction on daily activities and quality of life should be counterbalanced at the reduction in local recurrence risk. One has to be bare in mind however that accurate determination of tumour height is crucial. This implies that there is a need for standardizing endoscopy. When in doubt a soluble water-enema might give valuable information.

Another category patients that are possibly overtreated by 5x5 Gy are patients with early (stage I, pT1/2N0) rectal cancers. Again from subgroup analyses of the TME trial, we know that local recurrence is extremely rare and the impact of radiotherapy is non-significant (0.4% vs. 1.7%, P=0.091). An absolute difference of only 1.3% seems not enough to irradiate

every stage I rectal cancer patient. The problem is however that accurate diagnosis of early lesions prior to treatment is difficult.[59] Therefore, it is difficult during pre-treatment work-up to estimate the risk of local failure and the possible benefits of radiotherapy. Not only radiotherapy, but also major surgery might imply overtreatment for early lesions. It is known that lymph node metastases are seldomly engaged in this subset of rectal cancers indicating that lymphadenectomy serves hardly therapeutical or staging purposes. By performing local excision of early lesions the morbidity of laparotomy is avoided. This would imply a major step in reducing late morbidity as a large proportion of long-term dysfunction can be ascribed to TME surgery, and not to radiotherapy. Local excision of even pT1 tumours may however be associated with unacceptable high local recurrence rates up to 26%.[60] Ending up with a local failure after treatment of an early lesion is hard to sell. To minimise the risk of such catastrophes, accurate staging is of utmost importance in order to avoid local procedures for advanced lesions.[61-63]

Improving survival

As mentioned earlier, pre-operative radiotherapy decreases local recurrence risk but has no survival benefit in TME treated patients. Local recurrence is thought to affect survival, but apparently, an absolute difference of "only 5.3%" is too small to impact on survival. Moreover, distant failure is accountable for mortality and is substantial regardless radiotherapy (25.8% vs. 28.3%, P=0.387). So far it is unknown whether adjuvant chemotherapy which is standard in colon cancer patients with nodal involvement, may improve survival in rectal cancer patients that have been treated with 5x5 Gy and TME. In the past adjuvant treatment has proven to be ineffective for rectal cancer patients.[64] This was however in the era of conventional surgery when local recurrence risk was major. Now that local failure is no longer a confounding factor due to the beneficial effects of both TME and radiotherapy, the matter needs to be addressed again. The SCRIPT (Simply Capecitabine in Rectal Cancer after Irradiation Plus Tme) Trial randomises stage II/III rectal cancer patients that have had 5x5 Gy plus TME between oral capecitabine and observation. Unfortunately, trial accrual is slow leaving this important question unanswered. In the mean time more effective chemotherapeutics have been introduced in the field of colon cancer[65,66], opening possibilities for new clinical trials. An important difference with previous trials in the past decades is that pre-operative work up has become more accurate. Digital examination has been replaced by endoultrasound and MRI in many centers, leading to distinction between lesions that may be removed by either local excision, laparotomy or only after short term or prolonged neoadjuvant treatment. This development calls for inventive trial designs with adequate power to answer multiple questions.

Minimising the risk of symptomatic anastomotic leakage

Multimodality treatment of rectal cancer aims for adequate local control and prolonged survival. Apart from side late side effects on bowel, sexual and bladder function, acute morbidity

is important as well. In chapter 2 the acute side effects of radiotherapy using a 2 portal technique are extensively described. In the mean time, technique has changed substantially and Marijnen et al.[67] concluded, after describing the acute side effects of 5x5 Gy in the TME trial that "preoperative hypofractionated radiotherapy is a safe procedure in patients treated with TME surgery, despite a slight increase in complications when compared with TME surgery only." Indeed, apart from perineal wound dehiscence in APR patients, there are no significant clinical acute side effects that can be ascribed to radiotherapy. Apart from postoperative death, the most important complication after rectal surgery is anastomotic failure. There was no significant difference between irradiated and non-irradiated patients (10.9% versus 12.3%, P = 0.517).[68] Nevertheless, the rate of leakage is substantial, calling for further action. According to the multivariate analysis of the TME trial, both the construction of a temporary stoma and the placement of a drain in the presacral space are the only two factors correlated with a lower risk for leakage. It is noteworthy that there is no unanimous policy considering these two issues among surgeons in the Netherlands. Therefore, a national working party has been installed in order to reduce the morbidity and mortality associated with symptomatic leakage throughout the Netherlands. Guidelines will be evidence-based. Important questions that need to be asked for the individual rectal cancer patient are: what is the estimated risk for leakage prior to surgery (location of the tumour, gender, nutritional state etc.)? Is it possible to decide prior to surgery and not during surgery whether a stoma needs to be constructed (bowel function prior to multimodality treatment, likelihood of stoma reversal in a second procedure etc.)?

Laparoscopic resection of rectal cancer

Without elaborating on this hot topic, few words must be side on laparoscopy as surgical treatment of colorectal disease. For both benign and malignant diseases of the colon, laparoscopy is increasingly performed. The reported advantages are earlier recovery of bowel function and shorter hospital stay, improved quality of life without compromising oncological outcome.[69,70] Even despite perioperative optimization of open surgery using enhanced recovery programs, length of hospital stay is lower following laparoscopic surgery.[71] Moreover, the costs of the laparoscopic approach are only marginally higher than of open surgery.[72] Schwenk et al.[73] recently stated in a Cochrane systematic review including 25 randomised controlled trials that laparoscopic colonic resection "shows clinically relevant advantages in *selected* patients". Indeed, it is likely to assume that laparoscopy, especially in the early phase of the individual surgeon's learning curve, is only proposed to patients who are not likely to suffer from major postoperative complications. Moreover, many reports are from single-center institutions that have been able to gain a wide experience in laparoscopic colon resections. Finally, not only length of hospital stay should be of interest. The local infrastructure for postoperative care after hospital discharge should be accounted for as well: is the patient staying at home

without any (para)medical help or is he staying at "recovery hotels" hiring qualified nurses, therapists and home aides to meet all the patient's needs?

Rectal cancer seems a different entity. Considering its location in the lesser pelvis, it's a technically more demanding procedure requiring a long learning curve. Reports on laparoscopy are almost exclusively from non-randomised studies executed in experienced centers. Nevertheless, short term outcome may not always be as favourable (anastomotic leakage up to 17%)[74], and functional outcome may be unsatisfactory.[75] Laparoscopy is said not entail any oncological disadvantages.[74] However, focussing on the technical aspects of laparoscopy should not obscure the need for detailed preoperative work up, leading to unacceptable rates of palliative resection up to 25%[76], increased rates of positive resection margins[77] and local recurrence rates of 21%[78], putting us back in time when blunt dissection of rectal cancer was the norm. In conclusion, prior to introduction of laparoscopy for rectal cancer on a large scale, randomised controlled trials need to be awaited (COLOR II amongst others), surgeons need extensive training, and preoperative work-up should be standardized.

QUALITY ASSURANCE

Everyone involved in the treatment of cancer aims for improved treatment outcome. A tool to accomplish this goal is to increase the quality of the services that are delivered to cancer patients. For both gastric and rectal cancer, quality is increased by achieving good locoregional control. Achieving adequate local control is a matter of team work: radiologists play a profound role in preoperative imaging of rectal cancer, radiation and medical oncologists decrease tumor burden in case of locally advanced disease by administering prolonged chemoradiation, increasing the likelihood that the surgeon can perform a curative resection.

For gastric cancer, there are wide variations in outcome, calling for intervention. One possible way to improve quality, is to increase case volume, especially as surgery is the cornerstone of the treatment of gastric cancer. The literature on the relationship between volume and outcome is extensive and beyond the scope of this concluding chapter. It was Luft[79] who first explored the relationship in 1979 and concluded that there was a strong inverse relationship between hospital volume and mortality. Not many years ago, Birkmeyer[80] et al. investigated cardiovascular procedures and major cancer surgery and concluded accordingly. The mechanism of this persistent relationship is not completely understood. Possible confounding factors are the availability of well equipped staff and medical services, high quality of postoperative (intensive) care, and last but not least training of medical staff. Considering the latter, well-trained expert surgeons tend to work more often in high-volume hospitals, being prepared to focus on a relatively small area of surgical practise, troubling the volume-outcome relationship. Now that surgery for benign gastric diseases has become

a rarity and the incidence of gastric cancer is dropping, it is difficult to gain a certain level of expertise in gastric cancer treatment All together, for gastric cancer, concentrating cases in expert institutions seems the most logic means to improve nationwide outcome. Before appointing these expert centers, insight must be gained in the results of each treating center. In the United States the National Cancer Data Base (NCDB) collects detailed information on demographic and tumour statistics as well as treatment outcome for each cancer case in the US. Each year, every participating hospital receives a detailed and confidential report indicating how "good or bad" the center performs in comparison to regional and national benchmarks. This national non-governmental initiative has been a resource of cancer epidemiology throughout the years[81,82] and serves as a huge source of information for the benefit of quality assurance initiatives. Noteworthy is the low budget of 1-2 million dollars for maintaining this nationwide database.

In parallel, in Sweden, the Swedish Cancer Register has been introduced, making it mandatory by law(!) for each surgeon and pathologist to report each new cancer case including the surgeon and assistant surgeon who are involved in the treatment as well as information on surgical treatment (i.e. type of resection, curative intent, general and surgery-related postoperative complications etc.) Moreover, follow-up must be reported each year. Each year feedback on treatment outcome is given to all units. The Rectal Cancer Registry in Sweden has run for 9 years now and has included over 13.000 patients, from each center at least hundreds of patients. Now it has become possible to draw conclusions for each center, based on median results of specific endpoints. When centers do not reach standards, set by the surgical community, they may consider stop treating rectal cancer patients or seek additional training. Working in this way, treatment outcome improves. Although it is encouraging to see that trial results are superior to historical controls[83], it is important to realise that the majority of cancer patients is treated outside the framework of clinical trials. These patients also need to benefit from ongoing developments as well.[84,85] Finally, extensive training by experts is a prerequisite of improving treatment outcome: the acknowledgement that local recurrence of rectal cancer was a major problem in Sweden urged the medical community to acquire the TME technique by building up a training program and hiring Mr Heald, pioneer in TME surgery who teached this new surgical technique throughout Sweden. Similar initiatives were undertaken successfully in the Netherlands and Norway.[86,87] Yet, there is major room for further improvement, illustrated by the aforementioned challenges in rectal cancer treatment. In an attempt to meet challenges, a multidisplinary approach is necessary as is being employed currently in the Pelican Center Foundation, Basingstoke UK[88,89], offering training courses on colorectal malignancies applying MRI scanning in the preoperative work-up. Also, from economic point of view, it makes common sense to invest more in multidisciplinary training: Phil Quirke[90] calculated that the costs of multidisciplinary training in rectal cancer treatment amount only £200 per patient. Evidence shows a 20% reduction in cancer deaths through extensive training, making the total costs of each life saved £1000. For comparison,

by the introduction of novel chemotherapeutics as irinotecan and oxaliplatin the median survival of patients with metastastic colorectal cancer has improved over the past decade from 12 months (fluorouracil) up to 21 months.[91] Although these advances are commendable, the costs of the initial 8 weeks of treatment have increased 340(!)-fold from US$ 63 to US$ 21.033.[92]

In order to employ our resources in our struggle against cancer effectively, national cancer plans are crucial. Urged by the long waiting lists and worst treatment records in Europe, the United Kingdom launched the NHS Cancer Plan in 2000. Australia, Canada and New Zealand also have plans in place. France acknowledged the need for a comparable plan in 2003 and set up the National Cancer Institute (known as the INCa) employing 185 staff members within 6 months. The INCa initiated a cancer plan with a total of 70 key areas, all being precisely funded and evaluated. An expert committee lead by David Kayat, a medical oncologist and leading figure in France, calculated how much execution of the plan would cost. They asked the government for 1.7 billion euros, and they received the grant. It is a major plan including various measures: centralisation of basic research into 7 large regional research centers and structural coordination of cancer care. There is also room for raising the price of tobacco and buying the tobacco industry off, as well as for funding of television campaigns on the dangers of sun exposure. In 2004, a national plan against cancer was formulated in the Netherlands focusing on prevention, screening and treatment. Although the initiative is laudable, no concrete measures are taken considering organisation, funding and implementation. Putting pens to paper is not enough, long term vision and adequate funding is the key.

In conclusion, now that cancer mortality will overtake death from cardiovascular disease within a couple of years (http://www.kwfkankerbestrijding.nl/), it is time to decide how we will strike back as effectively as possible. When treating solid malignancies, setting up multidisciplinary teams involving organ-related specialists seems the key, with an emphasis on surgical training in technically demanding procedures as gastric and rectal cancer surgery. Within the EORTC, unfortunately there are no longer funds available for surgical quality assurance. The importance is however acknowledged: the European Journal of Surgical Oncology devoted a complete issue in august 2005 to the benefits of surgical QA. Recently, the European Society of Surgical Oncology released additional funds for surgical fellows, backing up this important area of surgical research. If governments are seriously willing to meet the challenge of combating cancer, investing in meaningful cancer plans and multidisciplinary training seems the only way.

SUMMARY

Cancer is a world wide health problem. Each year 10.9 million people are diagnosed with cancer. It is estimated that worldwide 24.6 million people are alive who have received a diagnosis of cancer in the last five years. In Western countries cancer incidence is increasing rapidly. In 2002, there was a cancer incidence in Europe of 873,700 cases, in Northern America of 1,570,500 patients (http://info.cancerresearchuk.org/cancerstats/). Of all malignancies solid tumours constitute the vast majority. Bowel, breast, lung and prostate cancer account for nearly half of all new cases.

Improving the quality of care aims at improving locoregional control, and thus survival. Numerous initiatives have been successfully employed in order to improve quality of radiotherapy and medical oncology. Although surgery is generally acknowledged as the mainstay of the treatment of solid tumours, surgical research encounters important difficulties: pharmaceutical companies do not release substantial funds to promote surgical research, neither seem governmental institutions willing to support trials investigating differences in surgical techniques. This possibly relates to the fact that every operation is considered a unique event which may hinder standardisation, a vital part of research when testing new treatment regimens. There is however a need for standardisation and uniforming surgical treatment: by controlling surgery, heterogeneity in patient outcome, caused by variation in surgical treatment, is removed as much possible. There are not many clinical trials that have made serious efforts to standardize surgery in order to reduce its confounding influence of surgery on treatment outcome. The Dutch D1D2 Gastric Cancer Trial[4,93] and the TME trial[94], both prospective randomised trials, have done their utmost to instruct surgeons onsite, to teach and control surgical treatment and to record every vital treatment detail.[95,96] The D1D2 trial investigated the role of extended lymph node dissection (D2) compared to limited lymph node dissection (D1) in patients with gastric cancer. The Dutch TME trial tested short term preoperative radiotherapy in rectal cancer patients who were treated with TME (Total Mesorectal Excision). The current thesis focuses on both trials.

Chapter 1 serves as a general introduction, describing the background and the outline of this thesis.

Chapter 2 is a review of the various aspects of gastric and rectal cancer treatment. Although the need for standardised and quality-controlled surgery is emphasized, the value of adjunctive treatment regimens is discussed as well.

Chapter 3 is an editorial that was released in the Journal of Clinical Oncology, reflecting upon a Japanese study (published in that same issue) that investigated the value of adjuvant chemotherapy in gastric cancer patients. 252 serosa negative gastric cancer patients were

randomised in a phase III trial between intravenous mitomycin, fluorouracil and cytarabine, twice weekly for the first 3 weeks after surgery followed by oral FU for the next 18 months (arm 1) versus surgery alone (arm 2). The primary end point was relapse-free survival. According to Japanese practise, 98% underwent extended lymphadenectomy (D2 dissection) and relapse-free survival was impressive: 88.8% resp. 83.7%. Remarkably, only 2 patients (none in the combination-treatment group, 2 in the surgery alone group) developed a local recurrence. These favourable results are beyond any expectation when treating Western gastric cancer patients. The editorial deals with differences in disease stage, surgical technique and type of chemotherapy that may explain these gross differences between Japan and Western countries.

In *chapter 4* the value of the "Maruyma Index of Unresected Disease" is studied. It was concluded in both the British MRC trial as well as the Dutch Gastric Cancer Trial (both large prospective randomised phase III trials) that there was no benefit from extended lymph node (D2) dissection in gastric cancer patients. However, postoperative mortality was substantial in the D2 arms of both trials, which possibly obscured a survival benefit of extended lymph node dissection. There are several ways to reduce the risk of postoperative mortality: according to subgroup analyses of the Dutch Gastric Cancer Trial, patients older than 70 years have substantial risk for postoperative mortality, making them less suitable candidates for extended surgery. Also, the risk of postoperative complications is reduces when spleen and pancreatic tail are preserved. Meanwhile, organ preservation techniques have been introduced successfully.Moreover, resection of these organs is no longer considered necessary for adequate nodal clearance. Finally, prevention of unnecessary resection of tumour negative nodes minimises the risk of postoperative complications as well. The question is however, how nodal clearance can be limited without compromising both staging and survival. The Maruyama program offers a possible solution. The program requires entry of 7 patients and tumour characteristics of an individual patient and then simply matches this case with very similar cases previously treated at the National Cancer Center Hospital in Tokyo, Japan. In this manner the computer gives a prediction of the likelihood of nodal involvement of each of the 16 lymph nodes stations. The Maruyama Index of Unresected Disease (MI) was defined as the sum of regional nodal disease percentages for stations that were not removed by the surgeon. The MI was introduced for the first time by the investigators of the SWOG trial that showed that postoperative chemoradiation was beneficial in gastric cancer patients. The MI turned to be a prognostic factor and stressed that there was substantial undertreatment in this US trial. Chapter 4 describes the value of the MI in 648 patients of the Dutch Gastric Cancer Trail who underwent a curative resection. According to the multivariate regression analysis, MI turned out to be a significant independent predictor of overall survival and disease-free interval. (HR 1.45, P = 0.016 resp. HR 1.72,, P = 0.010). The MI enables the surgeons to match the extent of surgical resection with the extent of regional disease. Obtaining a low MI seems

preferable in stead of dissecting the complete N2 echelon, exposing patients to substantial risks of postoperative death. The next step is prospective testing of the value of the MI.

Chapter 5 has tested a model that serves as a predictor of survival after gastric cancer treatment. Apart from treatment (surgery and its extent, adjuvant (chemo)radiotherapy etc.), there are other factors such as age, sex, the stage of disease at presentation and tumour location and morphology that determine a patient's prognosis. Current staging modalities focus solely on tumour depth (T stage) and the presence of nodal involvement (N stage). Nomograms are models that integrate other prognostic factors as well. One could argue that the need for adequate prognosis clinically irrelevant, as there is no role (yet) for adjuvant treatment in the Netherlands. However, both patients and doctors have a growing interest for individual-based specific information on survival prognosis. The nomogram sees to this need. The nomogram that was developed for gastric cancer was tested in only one high-volume US center (Memorial Sloan Kettering Cancer Center, NY, USA). We attempted to validate the nomogram in patients included in the Dutch Gastric Cancer Trial. Also, the discriminating value of the nomogram was studies in relation to the AJCC staging system.

There were 459 eligible patients with available information for the nomogram calculation. Nomogram discrimination was superior to that of AJCC stage grouping (concordance index 0.77 vs. 0.75, $P < 0.001$, Z-test) and proved to be an accurate predictor of 5- and 9 year disease-specific survival. Moreover, patients within different AJCC stages with heterogeneous prognosis were successfully discerned, using the nomogram. In comparison, the AJCC staging system that is presently used is unable to identify subsets of patients with homogeneous prognoses. By classifying patients according to differences in prognosis, suitable candidates for novel adjuvant treatment regimens may be identified. The nomogram is freely available in software from www.nomograms.org.

Chapter 6 describes a study that investigated risk factors for symptomatic anastomotic leakage after TME for rectal cancer. The benefits of TME are beyond any dispute: both local control and survival are superior compared to historical controls, and functional outcome (bladder and sexual function) has improved substantially through working under close vision of important nerve structures. Anastomotic failure remains however a significant problem. As anastomotic failure causes substantial morbidity and even mortality, all efforts should be directed towards the reduction of risk of anastomotic dehiscence.

Nine hundred twenty-four patients undergoing low anterior resection with primary anatomises were included in this study. Of all possible risk factors known from the literature, the presence of a diverting stoma (8.2% vs. 16.0%, RR 1.89 (1.24-2.90), P=0.003) as well as the placement of a drain in the pelvic area (9.6% vs. 23.5%, RR 2.53 (1.57-4.09, P<0.001) were correlated with a decreased risk of anastomotic failure. Interestingly, there were wide variations

in the policy regarding stoma construction and pelvic drainage, emphasizing the need for standardisation in order to avoid this major complication after TME.

Chapter 7 reports on the late side effects of both TME and short term radiotherapy. In the past, preoperative short term radiotherapy followed by conventional blunt dissection of the rectal tumour has been held responsible for increased bowel frequency, incontinence, urgency and emptying difficulties. We examined the late side effects in patients included in the TME trial. A questionnaire was sent to 708 patients who were alive and had no evidence of recurrent disease. 597 patients (87%) returned the questionnaire; the median follow up of responding patients was more than 5 years.

There was no difference between irradiated and non-irradiated patients regarding urinary function, stoma function and hospital treatment. However, irradiated patients reported increased rates of fecal incontinence (62% vs. 38%, P < 0.001), pad wearing due to incontinence (56% vs. 33%, P < 0.001), anal blood loss (11% vs. 3%, P = 0.004) and mucus loss (27% vs. 15%, P = 0.005). These data urge doctors to inform their rectal cancer patients reliably about the side effects of both radiotherapy and. Compared to radiotherapy, TME surgery is the main contributor to late bowel dysfunction. However, surgery is the only option that can lead to cure in contrast to radiotherapy that has merely benefits in terms of increased local control. The substantial additional long term side effect of radiotherapy on bowel dysfunction urges to tailor radiotherapy to those patients only who are most likely to benefit from it. However, pretreatment staging modalities presently used are not capable enough to accurately identify patients at risk for local failure.

Chapter 8 reports on the results of the TME trial after a median follow-up of 6 years. Early results after a median follow-up of 2 years showed a decrease in local recurrence risk (2.4 vs. 8.2%, P<0.001) in irradiated patients without any survival benefit (82.0% vs. 81.8%, P=0.84). It was hypothesized that there was no survival benefit yet due to a short period of follow-up.

There was a persistent significance in local recurrence risk at 5 years to the benefit of irradiated patients (5.6% vs. 10.9%, P < 0.001), yet there was still no survival benefit (64.2% vs. 63.5%, P = 0.902). Local failure is presumed to be a cause of death. However, an absolute difference of "only" 5.3% is perhaps too small to affect survival significantly. Moreover, distant failure occurs often regardless the administration of radiotherapy (25.8% vs. 28.3%, P = 0·387) and is an important cause of death.

In order to minimise the late side effects as described in chapter 7, subgroup analyses may be valuable. According to these analyses only tumours between 5 and 10 centimeters from the anal verge benefit from radiotherapy (3.7% vs. 13.7%, P<0.001). Local failure is uncommon in proximal lesions and the effect of radiotherapy is not significant (3.7% vs. 6.2%, P=0.122), making the "numbers needed to treat" in order to prevent one local recurrence substantial. For distal lesions there is neither any significant effect of radiotherapy (10.7% vs.

12.0%, P=0.578). An important confounding factor in distal rectal cancer is the considerable rate of circumferential resection margins. When tailoring the indications for radiotherapy by performing subgroup analyses on tumor height, it must be stressed that exact determination of tumour location, and thus the a priori chance of local failure is difficult.

The effect of radiotherapy depends also the stage of disease. According to subgroup analyses, only pTNM stage III rectal cancer (nodal involvement) benefit from radiotherapy. Apparently, with the involved nodes having removed, preoperative radiotherapy is able to treat (microscopic) nodal disease beyond the plane of surgical resection. Unfortunately, there are presently no reliable means that can be used in the preoperative work up that can identify patients with nodal involvement.

Short term preoperative radiotherapy achieves a relative risk reduction of 49% in local recurrence risk. Although there is no detectable survival benefit, this radiotherapy regimen remains a valuable treatment modality as the severe symptoms associated with local failure are prevented in many rectal cancer patients.

Chapter 9 reports on a benchmark study that was performed in order to evaluate multimodality treatment of locally advanced rectal cancer. The Catharina Hospital in Eindhoven, the Netherlands, is a national referral centre for rectal cancer patients in whom a radical resection is not likely to be obtained. All consecutive patients with a rectal tumour infiltrating into or less than 2 mm distance to the mesorectal fascia on MRI were included (n=252). For these lesions multimodality treatment is given involving prolonged radiotherapy of 50,4 Gy (1,8 Gy per fraction) and intra-operative radiotherapy (10-15 Gy) at the area of risk. Also, chemotherapy was administered (5FU and leucovorin, later replaced by oral capecitabine and oxaliplatin). Results of this multimodality treatment were compared to data from TME trial: patients with operable, mobile pT3/4 disease without distant failure at time of operation were used as a benchmark.

Three year local recurrence rate was significantly lower in TME trial patients: 5% and 17% (P = 0.0001). Interestingly, in as much as 83% of the patients wit locally advanced cancer a negative circumferential resection margin could be realised, compared to 75% of the TME trial patients (P = 0.037). Overall survival after 3 years was similar (76% for TME trial patients and 67% in case of locally advanced lesions, P = 0.071). Both circumferential margin status as lymph node status were important outcome parameters in both groups, for overall survival, metastases free survival and local recurrence. When chemoradiation is not able to achieve sufficient tumour down sizing and –staging, resulting in positive resection margins, the prognosis of patients of locally advanced lesions is considerably worse than of patients with operable disease with positive margins.

Chapter 10 is a review dealing with the role of sentinel node biopsy (SNB) in breast, gastric and colorectal cancer. SNB has been introduced to reduce the extent of axillary lymph

node dissection and thus the associated postoperative morbidity without compromising adequate staging, locoregional control and survival (breast cancer). Another advantage is the possibility to search the sentinel node for the presence of minimal residual disease (MRD) that might have prognostic influence. The review addresses the variation in technical aspects and outcome of SNB and MRD assessment. Considering the substantial variation in reported techniques there is a need for quality control leading to standardization of SNB and pathological examination to enable reliable comparison of studies. Only then a consensus regarding diagnostic and therapeutic strategies may arise.

Chapter 11 is a general discussion on future directions of gastric and rectal cancer treatment. Also a summary of the thesis is given.

Chapter 12 provides a summary in Dutch. Also, all centers that participated in the Dutch Gastric Cancer Trial and the TME trial are acknowledged.

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SAMENVATTING

Hoofdstuk 1

De kwaliteit van de gezondheidszorg staat onder voortdurende aandacht van de media. Ranglijsten van de "beste ziekenhuizen in Nederland" worden met enige regelmaat gepubliceerd en patiënten worden aangemoedigd met zorg hun dokter en/of ziekenhuis uit te kiezen. Ook de medewerkers in de gezondheidszorg zelf hebben kwaliteit hoog op de agenda gezet. De Inspectie voor de Volksgezondheid heeft in samenwerking met de Nederlandse Vereniging van Ziekenhuizen, de Nederlandse Federatie van UMC's en de Orde van Medisch Specialisten een aantal prestatie-indicatoren geformuleerd. Volgens de Inspectie zijn dit 'meetbare aspecten van de zorg die een aanwijzing geven over de kwaliteit, de veiligheid, de doelmatigheid en de toegankelijkheid van de zorg in ziekenhuizen.' Voorbeelden van prestatie-indicatoren zijn decubitusregistratie en –preventie, registratie van postoperatieve wondinfecties, percentage patiënten met een heupfractuur dat binnen één kalenderdag geopereerd wordt, percentage patiënten dat binnen 5 dagen na het eerste polikliniek bezoek voor een afwijking in de borst de uitslag goed- of kwaadaardig krijgt etc. Elk ziekenhuis is verplicht deze indicatoren te meten en rapporteren zodat deze voor (potentiële) patiënten, zorgverzekeraars en toezichthouders openbaar zijn. Men mag veronderstellen dat deze indicatoren bruikbaar zijn mits zij een natuurgetrouwe afspiegeling vormen van de kwaliteit van zorg, en bovendien aanzetten tot activiteiten die de kwaliteit van zorg vervolgens doen toenemen. Ten aanzien van het eerste is gesuggereerd dat dit op zijn minst twijfelachtig is gezien de beperkte kwaliteit van de aangeleverde data, de geringe accuraatheid van de meetmethode, de afwezigheid van correctie voor ziekteverscheidenheid en tenslotte de toevalsvariatie die een correcte interpretatie van prestatie-indicatoren bemoeilijkt.

Hoewel er uitvoerig gediscussieerd kan worden over de wijze waarop kwaliteit van de zorg het best gemeten kan worden, is het een aanlokkende en wellicht logische gedachte dat er enig verband bestaat tussen de kwaliteit en de uitkomst van de zorg. Echter, vooraleer men spreekt van kwaliteitsmeting in de zorg, is het wellicht verstandig het begrip kwaliteit eerst te definiëren. De 'van Dale' omschrijft kwaliteit als een 'bepaalde gesteldheid, een hoedanigheid, mate waarin iets geschikt is om voor een bepaald doel gebruikt te worden'. Indien men een medische behandeling tracht te kwalificeren is vergelijking met een standaard onontbeerlijk. Binnen de oncologische zorg zijn vele standaarden ontwikkeld die hun beslag hebben gekregen in richtlijnen en/of protocollen. Deze standaarden zijn gebaseerd op een multidisciplinaire consensus en gestoeld op wetenschappelijk verkregen bewijs. Een voorbeeld ter verduidelijking: specialisten in Europa die vanuit meerdere disciplines betrokken zijn bij de behandeling van patiënten met endeldarmkanker, zijn recentelijk overeengekomen dat het vervaardigen van een MRI scan, voorafgaand aan de behandeling, van groot belang is om de lokale uitgebreidheid van de kwaadaardigheid vast te stellen. Men zou kunnen stellen dat het achterwege laten van een MRI scan een slechte kwaliteit van zorg impliceert. Indien er op

vergelijkbare wijze consensus wordt bereikt over meerdere diagnostische en therapeutische trajecten, ontstaat er een referentiekader waarbinnen het medisch handelen getoetst kan worden. Het ontwikkelen van een standaard vereist de nodige inspanningen, maar kan grotendeels van achter het bureau plaats vinden. Echter, het vervolgens introduceren en handhaven van een tevoren vastgesteld kwaliteitsniveau is een veeleisende taak. Hiertoe zal een scala maatregelen nodig zijn variërend van goede registratie van behandeltrajecten, training van medewerkers in de zorg en, indien noodzakelijk, kwaliteit verhogende interventies. 'Quality assurance' oftewel 'kwaliteitsborging' omvat alle maatregelen die nodig zijn om een van tevoren vastgesteld kwaliteitsniveau te introduceren en vervolgens te handhaven.

Het behandelen van kankerpatiënten is 'team work'. Een optimale planning van het diagnostische en behandeltraject (inhoudelijk en logistiek) vereist de inbreng van meerdere specialisten. In geval van endeldarmkanker heeft de radioloog een belangrijke rol in het beoordelen van de MRI scan van het kleine bekken: de lokale uitgebreidheid van de tumor kan op deze wijze nauwkeurig beoordeeld worden waardoor van tevoren (tot op zekere hoogte) kan worden bepaald of de tumor volledig verwijderd kan worden (met negatieve (circumferentiële) resectie marges). Indien dit het geval is, zal de radiotherapeut conform de huidige landelijke richtlijn kortdurende radiotherapie (5x5 Gy) toedienen waarna de chirurg een TME (Totale Mesorectale Excisie) zal uitvoeren (zie later). Indien er volgens de MRI scan sprake is van lokale uitgebreidheid, komt de patiënt in aanmerking voor langdurige radiotherapie (50.4 Gy, 1.8 Gy per fractie), hetgeen de tumor in volume doet afnemen waardoor resectie met negatieve marges beter mogelijk wordt. In toenemende mate wordt aan dit radiotherapieschema chemotherapie toegevoegd, hetgeen het effect van de radiotherapie doet toenemen. Hierdoor ontstaat er ook een verantwoordelijkheid voor de medisch oncoloog in de diagnostische "work up'. Nadat de preoperatieve behandeling is voltooid, opereert de chirurg volgens de TME techniek waarbij onder zicht van belangrijke zenuwstructuren in het kleine bekken, de tumor inclusief het vet daaromheen wordt verwijderd. De patholoog onderzoekt het verwijderde weefsel en beoordeelt onder andere de doorgroei door de darmwand, de aanwezigheid van eventuele lymfkliermetastasen, en de radicaliteit van de resectie. Het mag duidelijk zijn dat een dergelijke multidisciplinaire benadering resulteert in een behandeling die duidelijk op de individuele patiënt is toegespitst.

De specialisten die in engere zin betrokken zijn bij de behandeling van patiënten met solide tumoren zijn de chirurg, de radiotherapeut en de medisch oncoloog. De chirurg levert, om begrijpelijke redenen, de grootste bijdrage aan de genezing van kankerpatiënten: het grootste deel van de 'tumour load' kan immers niet anders dan op chirurgische wijze verwijderd worden. De radiotherapeut en de medisch oncoloog dragen "slechts" bij aan een relatief geringe toename van locoregionale controle en overleving. Kwaliteitsverbetering door protocollering en standaardisatie vindt reeds lange tijd plaats bij de radiotherapeuten en medisch oncologen. Voor de chirurgie ligt dat beduidend anders. Het toedienen van een bestraling dan wel chemotherapie is redelijk uniform en in zekere zin goed reproduceer-

baar. Een operatie echter is een vorm van behandeling die onvoorspelbare elementen in zich draagt: elke patiënt is uniek met de nodige anatomische varianten. Bovendien kunnen onverwachte gebeurtenissen het beloop en resultaat van een operatie beïnvloeden. Dit zou het idee kunnen oproepen dat chirurgie niet te standaardiseren is en derhalve niet aan zekere kwaliteitstoetsing onderworpen zou kunnen worden. Het tegendeel is echter waar: in verschillende Europese landen (waaronder Nederland) is de TME techniek op grote schaal geïntroduceerd door middel van het trainen van chirurgen. TME resulteert in vergelijking met conventionele chirurgie (stomp verwijderen van de rectumtumor uit het kleine bekken) in lagere lokaal recidief percentages en verbeterde overleving, en is bovendien geassocieerd met betere postoperatieve blaas- en seksuele functie ten gevolge van het identificeren en sparen van belangrijke zenuwstructuren. Lange tijd is gedacht dat veel van de lokaal recidieven die ontstonden na de behandeling van endeldarmkanker, toe te schrijven waren aan het (agressieve) biologische gedrag van deze tumoren. Nu is het inmiddels duidelijk dat de kwaliteit van de (chirurgische) behandeling van grotere betekenis is. De resultaten van TME vormen het referentiekader waarbinnen de chirurgische behandeling dient te worden getoetst. Standaardisatie van chirurgie is niet alleen nodig om de kwaliteit van de behandeling te vergroten, te objectiveren en te toetsen. Het dient ook ter vermindering van de verschillen in de uitkomst van de behandeling. Dit is temeer nodig indien klinische studies worden geïnitieerd die de waarde van nieuwe chemotherapeutica moeten vaststellen. Nieuwe chemotherapeutica worden vaak opgenomen indien zij een relatief geringe verbetering laten zien ten opzichte van de tot dan toe geldende behandeling. (MOSAIC trial: toevoeging van oxaliplatin aan 5FU als adjuvante behandeling voor stadium II en III coloncarcinoom levert een toename op van 1.1% overall survival na 3 jaar: van 86.6% naar 87.7%, niettemin wordt dit regime in toenemende mate als standaardbehandeling toegediend). Het verstorende effect van de variatie in de chirurgische behandeling belemmert het accuraat vast stellen van het 'netto' effect van nieuwe, vaak veelbelovende maar ook dure geneesmiddelen.

Het huidige proefschrift kwam tot stand met financiële ondersteuning door de European Organisation of Research and Treatment (EORCT) te Brussel dat een fellowship ter beschikking stelde ten behoeve van "Quality assurance in surgical oncology". De Dutch Gastric Cancer Trial and de TME studie vormen de basis van dit proefschrift. De eerstgenoemde studie heeft de waarde van uitgebreide lymfklierdissectie onderzocht bij patiënten met maagkanker. Kwaliteit van de chirurgie werd gewaarborgd door intensieve training van chirurgen, 'on-site' instructie door ervaren chirurgen en gedetailleerde controle van chirurgische en pathologische gegevens door speciaal daartoe aangestelde trial coördinatoren. Uitgebreide dissecties worden veelvuldig toegepast in Japan, alwaar maagkanker de meest voorkomende vorm van kanker is. Kortweg geformuleerd, laten de resultaten van deze studie zien dat uitgebreide chirurgie (D2 dissectie) geassocieerd is met meer complicaties en postoperatieve sterfte dan beperkte chirurgie. Er is bovendien geen overlevingsvoordeel van D2 chirurgie. Wellicht dat er enig voordeel van D2 dissectie is indien postoperatieve sterfte gereduceerd kan worden.

De TME studie heeft de waarde van kortdurende preoperatieve radiotherapie (5x5 Gy) onderzocht bij patiënten met een mobiel rectumcarcinoom die geopereerd werden volgen de TME principes. Analoog aan de D1D2 studie werden de chirurgen uitgebreid getraind in deze nieuwe techniek. Bovendien werden ook de andere disciplines (radiotherapie en pathologie) onderwerpen aan een strikt kwaliteitsborgingprogramma.

Hoofdstuk 2 bevat een overzichtartikel over de diverse aspecten van de behandeling van maag- en endeldarmkanker. De noodzaak en voordelen van kwaliteitsborging van chirurgie worden benadrukt. Er is echter ook aandacht voor de veelbelovende ontwikkelingen op het gebied van radio- en chemotherapie.

Hoofdstuk 3 is een 'editorial', handelend over een Japanse prospectief gerandomiseerde studie die de waarde heeft onderzocht van adjuvante chemotherapie in maagkanker patiënten die uitgebreide chirurgie (D2 dissectie) hadden ondergaan. In totaal werden 252 patiënten gerandomiseerd tussen 'chirurgie-alleen' of chirurgie gevolgd door chemotherapie. Opvallend was dat van alle geïncludeerde patiënten er slechts 2 een locoregionaal recidief kregen, een uitstekend resultaat dat ongetwijfeld grotendeels valt toe te schrijven aan de uitgebreidheid van de lymfklierdissectie. Het editoreal bespreekt de ontwikkelingen op het gebied van maagkanker, bediscussieert waarom er een grote discrepantie bestaat tussen de Japanse en Westerse behandelresultaten, en beschouwt de rol van (neo-)adjuvante therapie in relatie tot de kwaliteit en uitgebreidheid van chirurgie.

Het verkrijgen van locoregionale controle bij de behandeling van patiënten met een maagcarcinoom is van groot belang. In Japan wordt dit gerealiseerd door het toepassen van uitgebreide lymfklierdissectie. Ondanks het feit dat de lange termijn resultaten van de D1D2 studie geen overlevingsvoordeel van uitgebreide dissectie aantonen, is er niettemin een voordeel van de D2 dissectie denkbaar indien de postoperatieve sterfte verder gereduceerd zou kunnen worden. Behoud van de pancreasstaart en milt lijken hieraan bij te kunnen dragen. Een alternatief behelst het voorkómen van onnodige dissectie van niet aangedane lymfklieren. Dit impliceert het preoperatief kunnen identificeren van de status van de regionale lymfklieren. Het zogenaamde "Maruyama Program" biedt hiertoe een mogelijkheid: het bestaat uit een Japanse database van 3843 maagcarcinoom patiënten en koppelt 7 patiëntkarakteristieken die allen pre-/peroperatief te bepalen zijn aan de waarschijnlijkheid dat de afzonderlijke lymfklierstations zijn aangedaan. Van alle patiënten in de D1D2 trial is bekend welke lymfklierstations werden gereserceerd. Als afgeleide hiervan werd voor elke patiënt de zogenaamde Maruyama Index of Unresected Disease (MI) berekend: een kwantitatieve maat voor de achtergebleven tumor load. De prognostische betekenis van de MI werd reeds eerder aangetoond in een grote Amerikaanse prospectief gerandomiseerde studie naar de waarde van adjuvante radio-chemotherapie. In *hoofdstuk 4* werd nagegaan of

ten eerste, deze MI van prognostische betekenis was in de D1D2 trial en ten tweede of het Maruyama Program dus gebruikt zou kunnen worden voor een op het individu toegespitste chirurgische behandeling.

Op grond van de beschikbare gegevens kon de MI berekend worden voor 648 van de 711 patiënten die curatief behandeld werden. De minimale follow-up bedroeg 11 jaar. De MI in D1D2 trial was aanzienlijk lager dan in de eerder genoemde Amerikaanse trial, wijzend op minder resttumor in de Nederlandse dan in de Amerikaanse trial. Bovendien bleek de MI, in tegenstelling tot de uitgebreidheid van de lymfklierdissectie (D1 vs. D2), van prognostische betekenis voor zowel de algehele overleving als de ziektevrije overleving.

Concluderend bleek de MI een maat voor de achterbleven tumor load. Bovendien had deze index prognostische betekenis. Aangezien de MI pre-/peroperatief bepaald kan worden, kan deze als leidraad gebruikt worden om niet aangedane lymfklieren in situ te laten. Zodoende kan postoperatieve morbiditeit en mortaliteit beperkt worden zonder de locoregionale controle en overleving te compromitteren. Met nadruk moet gesteld worden dat de waarde van de MI slechts retrospectief is vastgesteld, prospectief valideren is de volgende stap.

De uitgebreidheid en kwaliteit van de behandeling van patiënten met maagkanker bepaalt in grote mate de prognose van deze patiënten. Ook andere factoren zoals leeftijd, uitgebreidheid van ziekte, tumorlocatie en –differentiatie spelen echter een grote rol. De huidige wijze van stageren (TNM classificatie) concentreert zich 'slechts' op doorgroei van de tumor door de maagwand (T-stadium) en de eventuele aanwezigheid van lymfkliermetastasen. Zowel patiënten als artsen hebben in toenemende mate behoefte aan zo nauwkeurige prognosebepalingen. Het zogenaamde nomogram biedt soelaas: een nomogram is een voorspellend model waarin alle factoren worden meegewogen waarvan bekend is (op grond van multivariate analyses) dat zij prognostische betekenis hebben. Het nomogram voor maagcarcinoom patiënten werd ontwikkeld in het Memorial Sloan Kettering Cancer Center, New York, VS. *Hoofdstuk 5* beschrijft een validatiestudie waarbij het nomogram dat zijn waarde slechts had getoond in 1 Amerikaans ziekenhuis, werd getest in patiënten uit de D1D2 studie (patiënten afkomstig uit 80 ziekenhuizen). Tevens werd het discriminerend vermogen van het nomogram vergeleken met die van de tegenwoordig gehanteerde AJCC stadiering.

Er waren 459 patiënten van wie allen gegevens beschikbaar waren die nodig waren voor het calculeren van het nomogram. Het nomogram bleek een beter discriminerend vermogen te hebben dan de AJCC stadiëring (concordantie index 0.77 vs. 0.75, $P < 0.001$, Z-test). Het bleek bovendien een nauwkeurige voorspeller van de ziekte-specifieke overleving. Bovendien was het nomogram in staat om patiënten die door de AJCC stadiëring een zelfde prognose toegedicht kregen maar die feitelijk niet hadden, afzonderlijk te identificeren. Kortom, het nomogram is een goede voorspeller met adequaat discriminerend vermogen en kan wellicht in de toekomst gebruikt worden om high risk patiënten te identificeren die in aanmerking

zouden kunnen komen voor adjuvante therapie. Bovendien zijn nomogrammen bijzonder gebruiksvriendelijk en te downloaden via www.nomograms.org.

Hoofdstuk 6 beschrijft een studie naar factoren die risicoverhogend zijn voor het optreden van klinisch manifeste naadlekkage na TME. Hoewel TME resulteert in betere lokale controle en overleving in vergelijking met conventionele chirurgie, zijn er aanwijzingen dat er een groter risico is op naadlekkage. Dit hangt mogelijk samen met het verwijderen het mesorectum waardoor de bloedvoorziening van de naad gecompromitteerd kan raken. Een andere mogelijke verklaring is het feit dat ten gevolge van TME een ruimte achterblijft in de presacrale ruimte die opgevuld raakt met geïnfecteerd hematoom dat vervolgens doorbreekt in de genezende naad, hetgeen leidt tot een naadlekkage. Naadlekkage is verantwoordelijk voor veel morbiditeit en zelfs mortaliteit. Dientengevolge is het zaak alle mogelijke maatregelen te treffen teneinde het risico op naadlekkage te reduceren.

Van 924 patiënten uit de TME studie die een laag anterieure resectie hadden ondergaan werden alle mogelijke risicofactoren in kaart gebracht en bezien of er een correlatie bestond met het optreden van naadlekkage. Uit de multivariaat analyse bleek de aanwezigheid van een ontlastend stoma, alsmede de plaatsing van een drain in de presacrale ruimte de enige 2 significante factoren die waren gecorreleerd met een minder vaak optreden van naadlekkage (8.2% vs. 16.0%, RR 1.89 (1.24-2.90), P=0.003 resp. 9.6% vs. 23.5%, RR 2.53 (1.57-4.09, P<0.001). Bovendien waren deze 2 factoren geassocieerd met een gunstig beloop in geval van naadlekkage. Het is opmerkelijk te noemen dat er een sterk wisselend beleid bestaat beleid bestaat in chirurgisch Nederland ten aanzien van het aanleggen van stoma's en het plaatsen van drains. Er bestaat derhalve een noodzaak om meer standaardisatie aan te brengen teneinde de kans op het optreden van klinisch manifeste naadlekkage terug te dringen.

Hoofdstuk 7 handelt over de late effecten van preoperatieve radiotherpie (5x5 Gy) en TME bij patiënten die zijn behandeld wegens een rectumcarcinoom. Naast "harde" eindpunten zoals overleving en locoregionale controle ontstaat er in toenemende mate aandacht voor de functionele resultaten van de multidisciplinaire behandeling van patiënten met een rectumcarcinoom. Er werd onderzocht in welke mate defecatie- en blaasfunctiestoornissen bestaan bij patiënten met een mobiel rectumcarcinoom, die behandeld werden middels TME, al dan niet in combinatie met kortdurende preoperatieve radiotherapie. Tevens werd stomafunctie onderzocht en de tevredenheid van patiënten met defecatie en blaasfunctie. Lange termijn morbiditeit werd geanalyseerd bij patiënten die gerandomiseerd werden in de TME trial. Nederlandse patiënten zonder een lokaal en/of afstandsrecidief kregen een vragenlijst toegestuurd.

Vijfhonderd en zevenennegentig van de 708 aangeschreven patiënten (84%) retourneerden een ingevulde vragenlijst. Incontinentie voor feces kwam vaker voor bij bestraalde patiënten (62% vs. 38%, P < 0.001), evenals de het dragen van opvangmateriaal wegens deze inconti-

nentie(56% vs. 33%, P < 0.001). Bovendien was er vaker sprake van rectaal bloedverlies (11% vs. 3%, P = 0.004) en slijmverlies (27% vs. 15%, P = 0.005) in geval van radiotherapie. Bovendien voelden bestraalde patiënten zich meer beperkt ten gevolge van defecatiestoornissen in het ondernemen van dagelijkse activiteiten dan niet bestraalde patiënten. Er bestonden aanzienlijke blaasfunctiestoornissen die echter niet statistisch verschilden tussen bestraalde en niet-bestraalde patiënten.

Hoewel TME de mogelijkheid biedt tot het identificeren en sparen van zenuwen die van belang zijn voor een adequate blaasfunctie en defecatie, is er blijkbaar een aanzienlijke lange termijn morbiditeit van TME. Bovendien leidt kortdurende preoperatieve radiotherapie tot additionele defececatiestoornissen. Er dient echter opgemerkt te worden dat in deze studie een gezonde controlegroep ontbrak. Wellicht is een deel van de gerapporteerde functiestoornissen fysiologisch en derhalve leeftijdgebonden van aard. Niettemin kan worden gesteld dat er meer aandacht moet komen voor zenuwidentificatie en –sparing, en dat er nagegaan moet worden of het additionele nadelige effect van radiotherpie deels voorkomen kan worden door patiënten met een rectumcarcinoom selectiever te bestralen.

Hoofstuk 8 rapporteert de resultaten van de TME studie na een mediane follow-up van 6 jaar. De vroege resultaten na een follow-up van 2 jaar toonden een significante reductie in lokaal recidieven (2.4 vs. 8.2%, P<0.001) ten gunste van bestraalde patiënten. Er was echter geen overlevingswinst (82.0% vs. 81.8%, P=0.84), mogelijk ten gevolge van een korte follow-up duur.

Na 6 jaar bleek er sprake te zijn van persisterend significant verschil in lokale controle (5-jaars getallen: 5.6% vs. 10.9%, P < 0.001), echter nog altijd niet resulterend in een overlevingsverschil (64.2% vs. 63.5%, P = 0.902). Het is mogelijk dat een verschil van 'slechts' 5.3% in lokaal recidief percentages te klein om de overleving in gunstige zin te beïnvloeden. Bovendien komen prognosebepalende afstandsmetastasen veel voor, ongeacht of er sprake is van voorbestraling of niet (25.8% vs. 28.3%, P = 0.387).

Subgroep analyses kunnen van belang zijn om de waarde van preoperatieve radiotherapie beter te kunnen inschatten teneinde selectiever te kunnen bestralen. Er kleven echter ook nadelen aan subgroup analyses: de 'power' is vaak onvoldoende om statistische significantie aan te tonen dan wel te ontkrachten en 'subgroups' zijn bovendien voorafgaand aan de behandeling niet als zodanig betrouwbaar te onderscheiden. Derhalve dienen de resultaten van subgroup analyses niet zonder meer geëxtrapoleerd te worden naar de dagelijkse praktijk in een poging de indicaties voor preoperatieve radiotherapie te versmallen. Niettemin vormen deze analyses een vorm van 'evidence'. Volgens deze analyses hebben alleen patiënten met tumoren tussen de 5 en 10 centimeter van de anaalring baat bij radiotherapie (3.7% vs. 13.7%, P<0.001). Bij proximale laesies (tussen 10 en 15 centimeter) zijn lokaal recidieven relatief zeldzaam en is er bovendien geen significant voordeel van bestraling (3.7% vs. 6.2%, P=0.122). Bij distaal gelegen afwijkingen (tussen 0 en 5 centimeter) is er evenmin een effect

(10.7% vs. 12.0%, P=0.578). Bij deze laatste categorie patiënten is er echter vaak sprake van irradicale resecties (technisch moeilijke chirurgie laag in het kleine bekken), hetgeen een verstorend effect heeft op de waarde van preoperatieve radiotherapie: het is immers bekend dat radiotherapie niet effectief is indien er sprake is van positieve resectiemarges. Er moet echter benadrukt worden dat de exacte positie van de tumor en dus de a priori kans op een lokaal recidief moeilijk vast te stellen is: met enige regelmaat is er sprake van discrepantie tussen de bevindingen van endoscopie, CT, MRI en de bevindingen tijdens operatie.

Het effect van radiotherapie hangt mede af van het ziektestadium. Volgens de subgroup analyses hebben alleen de patiënten met lymfkliermetastasen (stadium III) baat bij radiotherapie. Blijkbaar is radiotherapie in staat om na resectie van aangedane lymfklieren microscopische restziekte buiten het chirurgische resectievlak adequaat te bestrijden. Helaas zijn er op dit moment onvoldoende (radiologische) middelen om de aan- of afwezigheid van lymfkliermetastasen voorafgaand aan de behandeling nauwkeurig te kunnen vaststellen.

Concluderend resulteert preoperatieve radiotherapie in een relatieve risicoreductie van 49% wat betreft lokaal recidieven (van 10.9% naar 5.6%). Gezien het ernstige klachtenpatroon dat samenhangt met een lokaal recidief, blijft kortdurende preoperatieve radiotherapie een waardevolle behandeling.

Hoofdstuk 9 beschrijft een 'benchmark' studie teneinde de gecombineerde behandeling met uitgebreide (chemo)radiatie, eventueel aangevuld met intra-operatieve radiotherapie te evalueren bij patiënten met een lokaal voortgeschreden rectumcarcinoom. Het Catharina Ziekenhuis in Eindhoven fungeert als verwijscentrum voor patiënten bij wie een radicale resectie (zonder voorafgaande behandeling) niet waarschijnlijk is. Patiënten met een tumor op een afstand van 2 of minder millimeter van de mesorectale fascie werden bestudeerd (n=252). De preoperatieve behandeling bestond uit langdurige radiotherapie met 50.4 Gy (1.8 Gy per fractie) en intra-operatieve radiotherapie (10-15 Gy) op het tumorgebied. Bovendien werd er neoadjuvant chemotherapie gegeven: aanvankelijk 5FU met leucovorin, later capecitabine and oxaliplatin. De resultaten van deze multi-modaliteit behandeling werden vergeleken met de resultaten van patiënten met pT3 rectumcarcinomen uit de TME trial die voorbestraald waren met 5x5 Gy.

Het lokaal recidief percentage na 3 jaar was significant lager in patiënten afkomstig van de TME trial: 5% vs. 17% (P = 0.0001). Opmerkelijk was dat 83% van de patiënten met locally advanced' laesies negatieve circumferentiële resectie marges (CRM) hadden versus 75% bij de patiënten uit de TME trial (P = 0.037). Overleving op 3 jaar verschilde niet significant: 76% in TME trial patiënten en 67% bij de patiënten uit Eindhoven. Zowel de CRM als de lymfklierstatus zijn voorspellend voor zowel de kans op een lokaal recidief als voor ziektevrije en algehele overleving. Indien ondanks uitgebreide voorbehandeling geen radicale resectie wordt verricht is er sprake van een zeer slechte prognose. Deze prognose is slechter dan bij patiënten uit de TME trial bij wie er sprake was van een positieve CRM.

Hoofdstuk 10 is een review die de rol van de schilwachtklierprocedure (SWP) bespreekt bij patiënten met een mamma-, maag- dan wel colorectaal carcinoom. Voor patiënten met een mamacarcinoom is de SWP geïntroduceerd teneinde de morbiditeit van een okselkliердissectie te reduceren zonder de stagering, de locoregionale controle en de algehele overleving te compromitteren. Een bijkomend voordeel is de mogelijkheid om de schildwachtklier te onderzoeken op de aanwezigheid op 'minimal residual disease' (MRD): de aanwezigheid van micrometastasen en geïsoleerde tumorcellen heeft wellicht prognostische betekenis. Wellicht hebben de patiënten met MRD een verhoogde kans op terugkeer van de ziekte. Het review behandelt de uitgebreide verschillen in techniek die bestaan om de schildwachtklier te identificeren en vervolgens te onderzoeken op de aanwezigheid van MRD. Gezien de grote variatie in de gebruikte technieken, kunnen er (nog) geen unanieme conclusies getrokken worden ten aanzien van klinische consequenties van de aanwezigheid van MRD. Derhalve is er behoefte aan gestandaardiseerde technieken. Alleen dan kan er een adequate vergelijking gemaakt worden tussen de resultaten van de vele studies die er op dit gebied gepubliceerd worden, waardoor een behandelconsensus ontstaat voor patiënten met MRD.

Hoofdstuk 11 bevat een algehele discussie ten aanzien van de huidige ontwikkelingen op het gebied van maag- en rectumcarcinoom. Tevens is er in dit hoofdstuk een samenvatting van dit proefschrift te vinden.

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CURRICULUM VITAE

Koen Peeters werd op 14 augustus 1972 geboren in Heerlen. In 1991 werd het Gymnasium β diploma aan het Bernardinuscollege te Heerlen behaald. Na te zijn uitgeloot voor de de studie Geneeskunde in Nederland, werd deze studie gestart aan de Katholieke Universiteit te Leuven, België. In 1992 (na voor de tweede maal te zijn uitgeloot) werd de overstap gemaakt naar Rechtsgeleerdheid aan de Rijksuniversiteit Leiden. In 1993 werd de propaedeuse voor deze studie behaald. Nadat ten derde male uitloting voor de geneeskunde studie een feit was, werd met succes de toen geldende bezwaarprocedure doorlopen waardoor toegang tot de studie Geneeskunde te Leiden werd verkregen. Het artsexamen werd cum laude behaald in 2000. Gedurende zijn studie werden meerdere assistentschappen doorlopen bij de vakgroepen Anaesthesiologie en Anatomie. Het afstudeerproject werd doorgebracht bij de vakgroep Pathologie (prof. dr. C.J. Cornelisse), alwaar onderzoek werd gedaan naar clonale heterogeniteit in het gemetastaseerde mammacarcinoom.

Na zijn afstuderen werkte hij bijna anderhalf jaar als assistent-geneeskundige niet in opleiding (AGNIO) bij de afdeling Heelkunde in het Groene Hart Ziekenhuis te Gouda. In februari 2002 werd aangevangen met het huidige promotieonderzoek. Hij ontving een EORTC Fellowship voor de periode van 2 jaar ten behoeve "quality assurance in surgical oncology" en bracht de eerste maanden van zijn onderzoeksperiode door op het Datacenter van de EORTC te Brussel, België. Na terugkeer in Leiden werd als AGIKO Heelkunde o.l.v. prof. dr. C.J.H. van de Velde verder gewerkt aan het huidige proefschrift waarbij zowel de Nederlandse D1D2 maagstudie als de TME studie de basis vormden.

In 2004 werd gestart met de opleiding Heelkunde in het Bronovo Ziekenhuis te Den Haag (opleider dr. A.B.B van Rijn, vanaf 2006 dr. H.J. Smeets). In 2008 zal hij zijn opleiding voortzetten in het Leids Universitair Medisch Centrum (opleider prof. dr. J.F. Hamming). Hij woont in Leiden samen met zijn vrouw Suzan en drie kinderen Wouter, Willemijn en Olivier.

NAWOORD

Evenals de behandeling van patiënten met kanker is het verrichten van wetenschappelijk onderzoek "team work". Zowel de "D1D2 studie" als de "TME trial" zijn unieke studies gebleken met een landelijk brede deelname vanuit meerdere disciplines. Het is dan ook meer dan terecht om een woord van dank uit te spreken naar alle specialisten die zich hebben ingezet om deze patiënten te includeren, alsmede naar alle patiënten die bereid zijn geweest tot deelname. Het opzetten en uitvoeren van een chirurgisch kwaliteitsprogramma binnen de genoemde studies heeft de nodige inzet vereist maar tegelijkertijd een schat aan informatie opgeleverd die mede de basis heeft gevormd voor dit proefschrift.

De actieve en kritische inbreng van alle auteurs bij het tot stand komen van de diverse manuscripten is van groot belang geweest. Dit geldt eveneens voor de ondersteuning van het Data Center van de afdeling Heelkunde in het LUMC waarmee het altijd prettig samenwerken was. Tenslotte een woord van dank aan de European Organisation for Research and Treatment of Cancer (EORTC) te Brussel die dit proefschrift heeft ondersteund door het verlenen van een tweejarig fellowship in "Quality Assurance".

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Mijn lieve Suzan, je geduld en liefde laat zich niet zo makkelijk vatten in één of twee regels…