Arne Wibe

# Rectal cancer treatment in Norway

URN:NBN:no-3453

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## Standardisation of surgery and quality assurance

*"Knowing is not enough; we must apply.*
*Willing is not enough; we must do."*
*Goethe*

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the Norwegian University
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Department of Surgery,
Department of Cancer Research
and Molecular Medicine,
N-7006 Trondheim, Norway



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**CONTENTS**

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Trondheim, September 2003

Arne Wibe

*To Tanja,*

*Anne Kathrine, Benedicte,*

*Jacob and Petter*

## LIST OF PAPERS

I) Wibe A, Møller B, Norstein J, Carlsen E, Wiig JN, Heald RJ, Langmark F, Myrvold HE, Søreide O, for The Norwegian Rectal Cancer Group. A national strategic change in treatment policy for rectal cancer - implementation of total mesorectal excision as routine treatment in Norway. A national audit. *Dis Colon Rectum* 2002; 45: 857-866.

II) Wibe A, Rendedal PR, Svensson E, Norstein J, Eide TJ, Myrvold HE, Søreide O, on behalf of the Norwegian Rectal Cancer Group. Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer *Br J Surg.* 2002:89:327-334.

III) Wibe A, Syse A, Andersen E, Tretli S, Myrvold HE, Søreide O, on behalf of the Norwegian Rectal Cancer Group. Oncological outcomes after total mesorectal excision for cure for cancer of the lower rectum: anterior versus abdominoperineal resection. Dis Colon Rectum 2003 (in press).

IV) Wibe A, Eriksen MT, Syse A, Tretli S, Weedon-Fekjær H, Carlsen E, Dahl O, Tveit KM, Wiig JN, Myrvold HE, Søreide O, on behalf of the Norwegian Rectal Cancer Group. Long-term outcome following standardisation of rectal cancer surgery on a national level – the effects of quality control and hospital caseload. Submitted.

These papers will be referred to by their Roman numerals.



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## ABBREVIATIONS

| | |
|---|---|
| APR | Abdominoperineal resection |
| AR | Anterior resection |
| CRM | Circumferential resection margin |
| LR | Local recurrence |
| RCT | Randomised clinical trial |
| TME | Total mesorectal excision |
| UICC | Union Internationelle Contre le Cancer |
| df | Degrees of freedom |

## DEFINITIONS

pTNM classification system (rectal cancer) [1]

The TNM system describes the anatomical extent of the disease, based on:

| | |
|---|---|
| T | the extent of primary tumour |
| N | the absence or presence of lymph node metastasis |
| M | the absence or presence of distant metastasis |

| | |
|---|---|
| T1 | Tumour invades submucosa |
| T2 | Tumour invades muscularis propria |
| T3 | Tumour invades subserosa or perirectal fatty tissue |
| T4 | Tumour invades adjacent organs or perforates visceral peritoneum |
| TX | Primary tumour cannot be assessed |

| | |
|---|---|
| N0 | No lymph node metastasis |
| N1 | Metastasis in 1-3 perirectal lymph nodes |
| N2 | Metastasis in > 3 perirectal lymph nodes [2] |
| N3 | Metastases in lymph nodes along superior rectal artery or other named vascular trunk [1] |
| NX | Lymph node metastases cannot be assessed |

| | |
|---|---|
| M0 | No distant metastasis |
| M1 | Distant metastasis |

| Tumour stages (UICC) [1] | | Dukes' stages [3] |
|---|---|---|
| I | T1-2, N0, M0 | A |
| II | T3-4 N0, M0 | B |
| III | $T_{any,}$ N1-3, M0 | C |
| IV | $T_{any,}$ $N_{any,}$ M1 | |

R-stage (Residual tumour stage) [1]

R 0 No residual tumour

R 1 Microscopic residual tumour

R 2 Macroscopic residual tumour

Circumferential resection margin (CRM)

The shortest distance (in mm) from the outermost part of the tumour to the resection margin. If macroscopic tumour deposits were noted in the mesorectum outside the main tumour, the measurement was made from the outer border of the deposit.

Involved circumferential resection margin

CRM ≤ 1 mm [4]

Rectal cancer

The definition of rectal cancer according to tumour level (distance from anal verge to the lower border of the tumour, measured on rigid proctoscope) varies between 10 and 18 cm from the anal verge [5]. Paper I and II included tumours within 16 cm from the anal verge. In paper III, on low rectal cancer, only tumours at or below 12 cm were included. Paper IV analysed rectal cancers within 15 cm from the anal verge. In the present work only adenocarcinomas were considered.

Mesorectum

The fatty tissue surrounding the rectum, containing rectal vessels and lymphatic tissue, enveloped by the mesorectal fascia [6].

Total mesorectal excision (TME)

TME is defined as a rectal cancer operation with sharp dissection under direct vision, preserving the mesorectum contained within an intact endovisceral (mesorectal) fascia. The TME procedure does not necessarily include resection of the entire mesorectum down to the pelvic floor/anal canal, as the standard policy for division of the rectal tube and the mesorectum is 5 cm below the tumour [6].

Conventional resection

A rectal cancer operation not fulfilling the TME criteria.

Anterior resection

A rectal resection and a colorectal or coloanal anastomosis.

Abdominoperineal resection

Removal of the rectum and anus and construction of a terminal colostomy.

Hartmann's procedure

Rectal resection with closure of the distal rectal tube and construction of a terminal colostomy.

General surgeon

A specialist in general surgery according to requirements set by national authorities.

Gastrointestinal surgeon

A specialist in general surgery and gastrointestinal surgery according to requirements set by national authorities. GI-tract surgery is a defined surgical speciality in Norway.

Curative intent

A major resection with a curative intent includes rectal cancer resections with the aim of cure, including patients with microscopic tumour involvement of any resection margin and/or patients having an intraoperative perforation of the tumour or bowel wall.

Curative resection

A major rectal cancer resection with the aim of cure, not including patients with microscopic tumour involvement of any resection margin, nor patients having an intraoperative perforation of the tumour or bowel wall.

Confounding factor

A factor distorting an association with the disease by being associated both to the disease and exposure variables (i.e. another risk factor or other risk factors) [7].

Univariate analysis

Simple data descriptions including plots, histograms, frequency and two-way contingency tables and risk analyses and survival analyses for one variable at a time.

Multivariate analysis

A statistical analysis describing interrelations among variables under study, and taking them into account simultaneously.

Sensitivity

The proportion of patients with the specific outcome who are correctly identified by the study test (a / a + c) (see later) [8].

Specificity

The proportion of patients not having the specific outcome who are correctly identified by the study test (d / b + d) [8].

Positive predictive value (PPV)

The probability that patients with a positive test have the specific outcome (a / a+ b) [8].

Negative predictive value (NPV)

The probability that patients with a negative test do not have the specific outcome (d / c + d) [8].

| | | Specific outcome Yes | Specific outcome No |
|---|---|---|---|
| Study test | Positive | a | b |
| | Negative | c | d |

a, true positives b, false positives c, false negatives d, true negatives

Examples: Study test positive = involved CRM
negative = uninvolved CRM

Specific outcome LR, distant metastasis, mortality

Local recurrence

Local recurrence (LR) is defined as recurrent disease in the pelvis, including recurrence at the site of the bowel anastomosis or in the perineal wound [9]. LR rates are given as the sum of LR occurring in isolation and concomitant with distant metastases.

## INTRODUCTION

The outcome after rectal cancer surgery in Norway was generally poor in the 1970's and 1980's, even for patients undergoing radical surgery. Data from the national university hospitals showed that 21% - 34% of the patients developed local recurrence (LR) in the pelvic area [10,11], with a 5-year survival of 55% [12]. For patients who developed local recurrence the 5-year survival was 8%. These national data were consistent with other international reports [13].

The poor results after radical surgery for rectal cancer, to a great extent caused by the detrimental effect of LR, have been regarded as an irrefutable fact even in contemporary literature [14]. Professional bodies have consequently advocated adjuvant radiotherapy, and more recently adjuvant chemoradiotherapy as standard treatment [15,16], as recommended by The National Cancer Institute in the US [17]. Such multimodal treatment is now given on a routine basis in many countries. Adjuvant radiotherapy can reduce the frequency of LR, but without any notable prolongation of survival [18]. The effect of adjuvant chemotherapy in rectal cancer treatment is also disputed [19].

Results after surgery for rectal cancer vary significantly, and variation in results seems to depend on the surgical performance [20]. This fact led to the notion that it ought to be possible to teach Norwegian surgeons better surgical techniques with a subsequent reduction in LR rate and better survival. Support for this view was primarily found in the study by Heald et al., reporting a 4% LR rate by surgery alone [21]. This result was held to be a consequence of optimised surgical technique and performance, emphasising a meticulous dissection in the anatomical plane surrounding the mesorectal fascia, which is the hallmark of total mesorectal excision (TME) [6]. This technique ensures that the main pathway of cancer spread (i.e. the mesorectum) is dissected out, removing the lymph nodes in the drainage area of the rectum. During the 1980's, some Norwegian surgeons had adopted the same technique and shown equally good result to that of Heald [22].

Thus there was reason to believe that better surgical technique (TME) would imply better oncological outcomes. Furthermore, it was argued that rectal cancer surgery should be performed by fewer and more specialised surgeons [23].

The surgical community in Norway decided in the early 1990's that TME should be recommended as the preferred technique for major rectal resections, and a national rectal cancer initiative was launched. The objectives of the project were to: 1) enhance the quality of rectal cancer surgery by introduction of TME, 2) reduce LR rates, 3) improve survival after curative surgery, 4) establish a quality control instrument (i.e. a rectal cancer registry) with feedback to participating institutions of their own results compared to the national averages.

The present work is a summary report on how a professional community in a few years can improve the outcomes of rectal cancer patients on a national level. By educating surgeons, theoretically and practically, improving routines for preoperative examinations and standardising the descriptions of pathological specimens, the clinical effectiveness of such strategic changes will be documented.

## AIMS OF THE STUDY

The main purpose of the present work was to evaluate the efforts taken by the Norwegian surgical community in order to promote and enhance the standards of rectal cancer treatment on a national level, in particular:

- to examine the outcome of rectal cancer surgery following implementation of total mesorectal excision as the standard rectal resection technique

- to explore the prognostic impact of the circumferential resection margin on local recurrence, distant metastases and overall survival following mesorectal excision

- to evaluate the oncological outcomes following mesorectal excision of cancer of the lower rectum, particularly the rates of local recurrence and overall survival for patients with tumours in this area

- to illustrate the influence of a rectal cancer registry as a quality control instrument on outcome of rectal cancer treatment, and furthermore,
  to investigate the rates of postoperative mortality, anastomotic leakage, local recurrence (LR) and overall survival related to hospital caseload among Norwegian hospitals during implementation of mesorectal excision.

## METHODOLOGICAL CONSIDERATIONS

### Organisation – "from conceptual framework to building competence"

Building on the initiative and network of a group of interested surgeons, the Norwegian Rectal Cancer Group was formally established in 1994. The group, with competence in gastrointestinal surgery, oncology, pathology and epidemiology, initiated a registry for rectal cancer, located at The Cancer Registry of Norway, a national population based cancer registry.

The Norwegian Rectal Cancer Project has received funding from The Norwegian Cancer Society, The Norwegian Medical Association, The Cancer Registry of Norway and from the Ministry of Health.

Every hospital in Norway performing rectal cancer resections was invited to join the collaborative group and assigned a contact surgeon to be responsible for registration and submission of data. As the aim of this initiative was to improve the surgical standard by implementing TME on a national level, a number of postgraduate courses were arranged at different hospitals in order to teach surgeons the TME technique. The Norwegian Surgical Society also recommended that certified surgeons should perform the rectal cancer surgery (gastrointestinal surgeons, an approved surgical speciality in Norway) [23]. The objective of this policy was that rectal cancer should be treated by fewer surgeons, i.e. "dedicated teams", specialised in rectal cancer surgery.

All the surgical departments treating rectal cancer were invited to submit clinical data to the Rectal Cancer Registry. Although there was no administative or "political" pressure upon them to participate, none refused.

Courses were also held for pathologists to increase the standard of both macroscopic and microscopic assessment of specimens, based on the method described by Quirke [4, 24, 25]. In addition, the standardisation of histopathology reports was emphasised.

## Study design

### "Optimised scientific design - a matter of ethics?"

Ideally, the clinical effectiveness of a presumed enhanced surgical performance should have been tested within an experimental randomised clinical trial (RCT) format. However, the prevailing view among opinion leaders in Norway was, and still is, that TME with its focus on standardisation of the surgical performance, a meticulous dissection technique laying the emphasis on removing the mesorectum as a “package”, was superior to conventional resection. Consequently it was concluded that optimisation of treatment, which clearly was needed, was a matter of surgical proficiency; and the most important factor – the surgeon – could not be controlled within an RCT.

Therefore, auditing the performances of individual institutions, preferably using a population based documentation system, was the way forward. It was also felt that an RCT with an alleged sub-optimal “conventional surgery arm” was unethical.

Such discussions, and the consensus reached, are interesting examples of how treatment policies are shaped; preferences and values may effectively block the opportunity to perform studies with an optimal research design, i.e. the RCT format. A more pragmatic approach, i.e. observational studies, can be an attractive research strategy for assessing health care interventions, as pointed out by Black [26, 27].

### Data collection

#### "Multiple sources"

The Rectal Cancer Registry acquires data from several sources. Surgical departments report demographic and clinical data on a specific form. Information from the histopathology assessments is extracted from the pathology departments’ obligatory reports to the Cancer Registry. Together with the compulsory reporting system from clinical departments to the registry, this ensures that every person with rectal cancer is identified. A unique 11-digit personal identification number, allocated to all citizens at birth, facilitates the tracing of individuals and ensures a complete follow-up.

Routine reminders sent to the surgical departments obtain information on follow-up, and information on deaths is transferred from Statistics Norway. At the latest update, information was available for patients diagnosed during the period November 1993 - December 1999.

**Quality of data**

**"Cross-checking procedures"**

The Rectal Cancer Project is population based (4.5 millions), and the collaboration with The Cancer Registry of Norway ensures the completeness of registration, as it is a compulsory reporting system for malignant diseases in Norway, both for clinicians and pathologists.

Follow-up information on adjuvant treatment, local recurrences and distant metastases are collected from different sources. Primarily such information is obtained by routine reminders to the contact surgeon at each hospital. In addition, data on local recurrences and distant metastases are checked against copies of histopathology reports sent to the Cancer Registry of Norway.

Post-mortem examinations have not been performed routinely. In a national population based project, it is not possible to be sure that every local recurrence or distant metastasis have been identified, as there may have been sub-clinical recurrences or metastases among patients dying of other causes.

The use of LR as the outcome measure is not without problems. First of all, there may be wide variations in LR rates depending on the definition of LR employed and the subgroups studied, i.e. LR rates can vary by manipulation of inclusion criteria. Here, *total LR* rates are used, i.e. LR occurring in isolation *plus* LR concomitant with distant recurrence. In addition, LR is a time dependent phenomenon, and to avoid the potential for underreporting or reporting bias, cumulative rates are also given.

Some authors use both overall and relative (cancer-specific) survival; bias might be a potential problem with the use of the latter, as it may depend on the rate of autopsy. The endpoint of overall survival cannot be manipulated, and all survival data used here is overall (crude) survival.

The research assistants were taught the concepts of surgical anatomy, operative procedures (including video demonstrations) and tumour staging. They visited hospitals as part of the follow-up and examined case notes and outpatient clinic information. Visits were mainly to hospitals where reporting and follow-up were slow. All patient records were evaluated by at least two project members.

**Running the project**

**" Feedback of results - monitoring treatment standards"**

Following regular updates and analyses by the project staff, the surgical departments have received their own results together with the national averages for comparison. However, the results of individual hospitals are anonymous to all but themselves and the project staff.

Some hospitals have asked for detailed data to explore and handle their potential quality problems. Thus, the feedback of results to each department has not only been used as a tool for quality assurance, but also as an incitement for individual appraisal.

Several steps have been taken to ensure a sustained focus on treatment standards. Workshops have included issues related to preoperative staging, dissection technique, pathological examinations and updated results. Surgeons, oncologists and pathologists from all parts of the country are invited to use data from the registry for scientific purposes. Recently, five "research fellows", one from each of the five health regions, have been recruited to analyse national data. Furthermore, all hospitals may use their own separate data for publishing. Such a policy has been important to consolidate a national co-operation.

## Statistical considerations

**"How to get the message through"**

Data were first analysed by descriptive univariate methods, such as frequencies, cross-tabulations and graphic inspections. Potential risk factors were examined by multivariate Cox proportional hazard regression models, both forwards and backwards, based on the assumption of proportional hazard rates for groups compared in the model. Initial levels of significance were 15%; finally the level of significance was set at 5%.

In paper I – III multivariate regressions were performed with all the significant variables analysed together. In paper IV the variables were examined separately, but adjusted for patient and tumour characteristics at the time of diagnosis. In paper III a stratified multivariate Cox model was used to describe the hazard of LR and cumulative overall survival for the two main variables, anterior resection and abdominoperineal resection, respectively. The same approach was used to describe the independent impact of different tumour levels. The main advantage of this method, compared to the univariate Kaplan-Meier analysis, is that the risk of the two variables is adjusted for other significant outcome predictors.

In paper II, the role of the circumferential margin as predictor of local recurrence was examined in a univariate regression model, illustrated by logarithmic curve estimation weighted by cases, (i.e. CRM groups with more patients count more than CRM groups with fewer patients). How well the model fits the data was given by $r^2$ (explained variance).

Sensitivity, specificity and predictive values are all time dependent figures, and thus they have to be judged in the light of median follow-up.

## SUMMARY OF PAPERS

**Paper I** examined the outcome of rectal cancer surgery during implementation of TME in the period November 1993 through August 1997. The results for patients treated by TME (n = 1395) were compared to outcomes following conventional surgery (n = 229). It was found that the risk of local recurrence decreased by half (from 12% to 6%) using TME compared to conventional surgery. Local recurrence was identified as a strong predictor of survival, and overall survival was significantly improved by TME. Furthermore, the study demonstrated three important points: 1) a refinement of the surgical resection technique for rectal cancer can be achieved on a national level, 2) the TME-technique can be widely distributed, and 3) surgery alone can give excellent results.

**Paper II** focused on the prognostic impact of the circumferential resection margin (CRM) on outcomes following mesorectal excision for rectal cancer. The cohort included 686 patients who underwent a TME procedure with curative intent in the period November 1993 through August 1997. The rates of local recurrence, distant metastases and mortality were significantly higher in the group of patients (n = 65) with a tumour involvement of the CRM, compared to the group of patients (n = 621) with a tumour-free margin. Concerning LR, a high specificity and the negative predictive value of an uninvolved (> 1 mm) circumferential margin may guide clinical practice, i.e. whether to use adjuvant postoperative radiotherapy or not.

**Paper III** analysed the outcomes following TME for rectal cancer of the lower rectum, particularly comparing the rates of local recurrence and overall survival after anterior resections (AR) and abdominoperineal resections (APR). In addition, tumour level was analysed as an independent predictor of outcome. The cohort included all patients (n = 2136) undergoing mesorectal excision in 47 hospitals during the period November 1993 through December 1999. The level of the tumour did influence the risk of LR, but the operative procedure, AR versus APR, did not. On the other hand, the operative procedure influenced overall survival, while the level of the tumour did not. The differences of LR rates for operative procedures and/or tumour levels could not guide the selection of patients for adjuvant radiotherapy. Intraoperative bowel perforation and tumour involvement of the circumferential margin were identified as independent prognostic factors, which were more common in the lower rectum, explaining the inferior prognosis for tumours in this region. These variables may guide the selection of patients for adjuvant therapy.

**Paper IV** focused on the influence of a rectal cancer registry as a quality control instrument on outcomes of rectal cancer treatment. The study also analysed the prognostic impact of hospital caseload and hospital status during implementation of mesorectal excision. The cohort included all patients (n =

3388) with a rectal cancer within 15 cm from the anal verge treated for cure in the period November 1993 through December 1999. Rectal cancer surgery was performed at 54 hospitals.

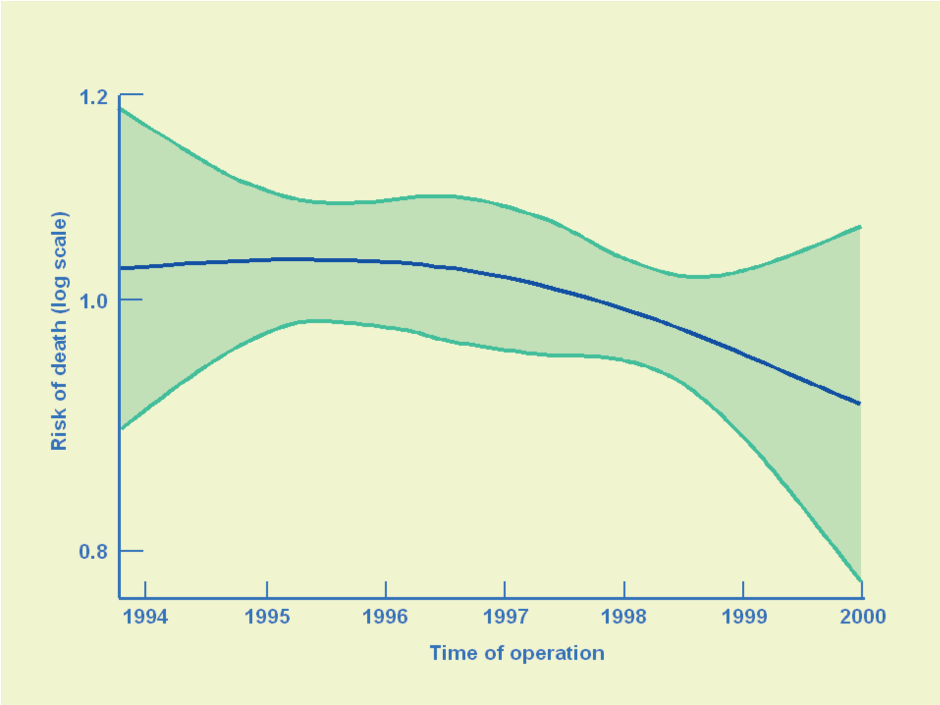
On a national level, there was an improved quality of surgery during the project, measured as a lowered risk of local recurrence. Monitoring treatment standards, with feedback of results to each hospital, seemed to improve quality of treatment (i.e. reduce rate of LR) in hospitals with an initial high rate of local recurrence.

The hospitals were divided into four groups according to their annual caseload. The rate of local recurrence was higher at low caseload hospitals compared to hospitals with high caseloads (annual caseload < 10 vs. ≥ 30), and the mortality risk was higher for patients treated at hospitals with an annual caseload less than ten compared to hospitals with caseloads ≥ 30. The risk of local recurrence was lower at university hospitals compared to local hospitals. Altogether, the study provided evidence that rectal cancer treatment can be improved by increasing hospital caseload, by better organisational focus on rectal cancer treatment and by establishing a rectal cancer registry monitoring treatment standards throughout the country.

Altogether, *the importance of surgical technique* in the treatment of rectal cancer was demonstrated by *paper I* as the benefit of TME compared to conventional surgery in its ability to reduce the risk of local recurrence and improve overall survival. *Paper II* scrutinised the close relationship between the circumferential margin and the occurrence of local recurrence, distant metastases and mortality, benchmarking *optimised surgical technique* as the most important step in order to cure the patient. *Paper III* showed that intraoperative perforation of the tumour or bowel wall, or an involved circumferential margin, which are more common in the lower rectum and which both may be related to *surgical technique*, most likely explain the inferior prognosis of low rectal cancer. *Paper IV* presented the overall improvements following implementation of an *optimised surgical technique* at a national level.

These four papers have focused on the positive effect of enhancing surgical competence and skill. In particular, they have documented the effect of TME on reducing local recurrence. However, the most important endpoint, and the ultimate question of cancer treatment, is how the strategic changes launched ten years ago have influenced overall survival. This may be answered by a smoothed splines regression analysis (df = 2) describing the relationship between the risk of mortality and time of operation (Figure 1). During the first years of the project the overall survival was unchanged, then after a few years a survival benefit is observed.

Figure 1. The risk of death according to time of operation (black line). (95% confidence intervals are given by the green lines).



## GENERAL DISCUSSION

Rectal cancer surgery has been characterised by a high incidence of local recurrence (LR). Numerous studies summarised in a review of more than 10.000 patients treated with curative intent by surgery only showed a median LR rate of 18.5% (range 3-50%) [13]. A striking phenomenon is that LR rates vary considerably among surgeons and hospitals. The consequence of LR is not only increased morbidity and suffering, but also a significant negative impact on survival [28].

Therefore, adjuvant and neo-adjuvant treatment strategies have been applied as standard treatment in many countries [15,16], particularly radiotherapy, either preoperatively or postoperatively, and either as a long course or a short course. In a recent review of 27 randomised trials, it was reported that adjuvant radiotherapy significantly improved local control, by 9% in absolute terms [18]. Survival benefit was 3%, although there was a 3% increase in treatment-related deaths among patients treated with short-course preoperative radiotherapy. It was concluded that the benefits from radiotherapy of improved local control do not fully translate into improved survival.

However, concerning strategies for the future, it may be wrong to draw firm conclusions from this review, as the studies included were undertaken before mesorectal excision was taken into use. It is likely that the benefit of radiotherapy will decline following an improved surgical standard. On the other hand, the radiotherapy regimens used in these series may not fulfil modern standards for adequate doses and/or field methods, and as discussed in a Swedish review [29], it may be argued that better radiotherapy regimens (preoperative radiation) are more effective and less toxic compared to earlier standards.

The Dutch Colorectal Cancer Group reported results following TME +/- radiotherapy [30]. Preliminary data showed that radiotherapy reduced the risk of LR also when administered to patients undergoing TME. The study left open the question of which patients benefit most from radiation therapy. However, that trial may not be comparable to the present studies, as the Dutch cohort did not include high-risk patients with fixed tumours, neither patients with previous or coexisting cancer, nor those who had previously undergone large bowel surgery, chemotherapy or radiotherapy for any reason.
Furthermore, the median follow-up was only two years in the Dutch study, and as we know that radiotherapy can postpone local recurrence [10], we should wait for the 5-year figures.

Another controversy is the adoption of chemotherapy for rectal cancer. In a randomised Norwegian study of 136 patients treated by conventional surgery in the period 1987-1991, postoperative radiotherapy combined with chemotherapy (5-fluorouracil) improved treatment results for patients in stage Dukes' B and C, in terms of local recurrence, recurrence-free survival and overall survival [31]. In the group of patients treated with adjuvant therapy, the rate of local recurrence was 12%, compared to 30% in the group with surgery alone. Even though an obvious benefit of adjuvant chemoradiotherapy was observed, such benefit may not occur following improved surgical standard.

Since 1990 the US National Institute of Health has recommended combined chemoradiotherapy for patients with Dukes' stage B and C [17]. Although the survival benefit of chemotherapy has been disputed [19], still the current debate focuses on the efficacy of adjuvant chemoradiotherapy, and the doses and timing of radiation [16]. Refinement of each form of therapy is thought to be the way forward. However, long-term complications, detrimental effects on bowel function, quality of life, the matter of resources and the time spent for treatment have to be kept in mind when comparing the almost negligible survival benefits [16].

The Norwegian surgical community chose a different strategy. Aware of the variability in surgical technique, which significantly affects outcome of rectal cancer, Norwegian surgeons decided to improve the standards of surgery through a national rectal cancer project. Knowing that LR is a most important factor predicting survival, it was focused on refinement of the surgical technique (the primary curative treatment) by implementing TME at a national level. A comprehensive educational program was launched, teaching surgeons the meticulous dissection, demonstrated by Mr. Heald during workshops in different Health Regions in Norway.

The main problem with this strategy - as alluded in the introduction - was the lost opportunity of a prospective randomised clinical trial (RCT), as the TME technique could not be controlled versus conventional surgery within an RCT setting. This issue was considered, but an RCT was thought to be unethical [32], as there was a body of evidence clearly indicating that optimal surgery was the clue to prevent LR [6, 21, 24, 25]. In addition, it was made clear that many leading institutions would not participate in an RCT in which "conventional surgery" was one treatment option.

Another controversy was the alleged technical complexity of the procedure; it was thought impractical to perform this technique outside specialist centres. To overcome this problem, it was recommended that rectal cancer surgery should only be performed by specialists in gastrointestinal surgery, or by those in training for this speciality, supervised by a certified specialist.

An important step was the increased focus on the histopathology assessments, emphasising the examinations of the circumferential resection margins.

Establishing a specific rectal cancer registry was the definitive tool for quality assurance of individual departments, and moreover, the feedback of their own results facilitated the investigation of possible quality problems.

The results described in **paper I** indicated that the national efforts to improve rectal cancer surgery headed in the right direction. The overall LR rate was clearly reduced compared to our national historical data, 13% versus 28%, at four and five years, respectively. Furthermore, the marked reduction of LR was followed by a substantial increase of overall survival, 67% versus 55% at four and five years, respectively; the latter group only included patients < 75 years [12].

Moreover, there were significant better outcomes for patients treated by TME compared to conventional surgery, supporting the central idea of the project; "optimal surgery is the most important prognostic factor in rectal cancer treatment".

These were the first important messages of the project, providing evidence that the choice not to perform a national RCT could be substantiated. A randomised study would have the consequence that more patients would be treated by conventional surgery, to the hazard of their lives.

Another important message could be voiced; the meticulous dissection of TME could be implemented on a national level, outside specialised centres, and become part of standard treatment. Thus, the national educational program had facilitated a centrifugal spread of competence, and a national change in treatment policy had been carried out.
Although not all the patients were treated by TME during these first years, even the group treated by conventional surgery had better outcomes than that reported by the historical audit, suggesting a stepwise learning process.

Some previous reports on TME surgery were single hospital series, and often a considerable amount of the patients was given radiation and/or chemotherapy. The strength of this study refers to the description of all rectal cancer patients in Norway diagnosed in the period November 1993 through August 1997. The frequencies of different treatment modalities explained the selection process of the study groups, confirming no selection bias. Radiotherapy was given to 8% and chemotherapy to 3% of the cohort. Thus, it was reason to believe that the overall results presented were based on improved surgical standard, and not by adjuvant therapy, neither by selection bias.

It may be argued that the study had short follow-up, with a median of 30 months. However, the level of evidence was high, as the confidence intervals were narrow, and the statistical analyses were consistent, whether it was univariate or multivariate procedures performed.

Furthermore, there were a large number of patients, surgeons and hospitals involved, supporting the applicability of TME in a routine setting.

**Paper II** took one step further to describe the relationship between the effect of a meticulous dissection technique and outcomes of rectal cancer surgery. Based on previous reports [4, 24, 25], focus was directed towards the impact of CRM to predict LR, metastases and mortality. During the project, pathologists were taught standardised handling and reporting of the specimens, according to the principles described by Quirke [4, 24, 25]. In this study, only TME specimens were included, and none of the patients were treated by radiotherapy, however, 3% of the patients had chemotherapy. The results confirmed the hypothesis that the shortest distance between the tumour and the resection margin, i.e. the CRM, is an important outcome predictor. Concerning local recurrence, the CRM can be used to select patients for adjuvant radiotherapy, as the high negative predictive value (95%) told us that only 5% of the patients with an uninvolved CRM (> 1 mm) developed LR. This was an important message, as 76% of the cohort was high risk patients (Dukes' stage B + C), and 5% had T4-tumours. Therefore, surgeons should maximise the probability of obtaining a tumour-free margin, also in the cases of advanced tumour status. In spite of the independent risk factors given at diagnosis, the most important ones are those that can be manipulated by surgery, like the CRM.

The strength of the messages in this paper was based on consistent univariate analyses, as well as multivariate regressions.

It has for long been argued that outcomes are less favourable for tumours located in the lower rectum, particularly tumours treated by APR [33 - 36]. Although many theories were proposed to explain this phenomenon, we did not know whether it was related to tumour level itself or an inherent consequence of tumour and treatment characteristics. But because of the significant variation of results among different surgeons [20, 37 - 41], it was hypothesised that treatment variables are most important for the prognosis of low rectal cancers, which constitute the greatest challenge to the surgeons. **Paper III** examined the outcomes of rectal cancer related to the level of the tumour, and furthermore, the relationship to the type of resection, AR versus APR, for patients treated by TME.

The analyses did not reveal any considerable differences of outcomes related to tumour level, neither to the type of resection. The LR rate only differed by 5 - 6% between levels and/or types of resection. In the multivariate hazard analyses adjusted for significant predictors, the risk of LR was identical for patients undergoing AR and APR when TME was performed.
In spite of reduced survival for patients with low rectal cancer, multivariate analyses did not expose a true significant prediction for tumour level; but type of resection was identified as an independent predictor of survival, as patients

undergoing APR had less favourable survival compared to patients treated by AR.

Furthermore, these analyses confirmed the significance of treatment variables for the prognosis of rectal cancer. Intraoperative bowel perforation and tumour involvement of the CRM were identified as independent prognostic factors, and these features were more common in the lower rectum. In fact, perforation of the tumour or bowel wall was four times more common during APR than AR, explaining the inferior prognosis for tumours in this region. This finding supported the main idea of the project, i.e. the surgical performance as the most important prognostic factor. Following these results, but in contrast to other studies [33], we do not recommend using level of the tumour or type of resection as indicators for selecting patients for adjuvant therapy. The risk of LR and mortality in the groups of patients with perforation and/or involved CRM may imply a recommendation for adjuvant therapy, although, we do not know the effects of radiotherapy and/or chemotherapy for those groups, so far.

The analyses in this paper illustrate the necessity of multivariate analyses to explain the causes of any difference revealed by univariate statistics. The difference of LR rates between the AR group and the APR group, although statistically significant, was cancelled out when adjusted for true LR predictors. Such analytical tools are necessary to avoid confounding, which is important for the decision of treatment strategies.

The results of this study support the significance of good surgical performance, and that cutting into tumour or an inadvertent perforation of the rectal tube implies inferior outcomes.

**Paper IV** took one step further to elucidate this theme. In these analyses the performance of all the Norwegian surgical departments handling rectal cancer surgery was assessed. Several studies have reported variations of outcome of rectal cancer surgery between single surgeons [20, 37 - 41]. This was not an issue of the present study. This national project, like the Dutch initiative, has advised specialised surgeons, preferably working within teams, to perform the surgery of rectal cancer, ensuring the quality of each procedure [42]. Therefore, it may be difficult to interpret the results of single surgeons, and it may also be the wrong signal to try to do so.

In particular, paper IV examined the differences in LR rates among Norwegian hospitals. The risk of LR was doubled in hospitals with the lowest caseloads, compared to hospitals with the largest caseloads. This difference was followed by an increased risk of mortality among patients treated at hospitals with low caseloads. Although, large caseload was no guarantee for optimal treatment, as some large hospitals were not performing very well, and vice versa, some minor hospitals had good results. Although a caseload effect for rectal cancer treatment could be identified, there had to be other important factors affecting outcome. Most likely, standards of the radiological and the pathological service, and the organisation of surgery, as well as individual surgical proficiency, may have influenced the overall quality of treatment at single hospitals.

A major issue of the national project was monitoring of treatment standards, providing the opportunity of intervention towards departments not fulfilling acceptable quality standards. Some of these hospitals with a quality problem received support, and later they obtained results comparable to the best group of hospitals.

Such progress was the main goal of the Norwegian Rectal Cancer Project, and as described by this paper, the national initiative launched ten years ago has improved treatment standards. Following implementation of an optimised surgical technique, the average risk of LR has declined, and during the period 1994 to 1999 this risk has been reduced by 50%.

## CONCLUSIONS

This work demonstrates that a national strategic change in treatment policy for rectal cancer can be undertaken, that postgraduate education of surgeons with centrifugal spread of competence can be performed, and the outcome of such initiatives can be audited. In particular it is described:

- that a refinement of the surgical resection technique can be achieved on a national level and that surgery alone can provide excellent results

- that the circumferential resection margin is an important prognostic factor that may guide the selection of patients for adjuvant therapy

- that the prognosis of low rectal cancer depends on treatment related factors, such as involved circumferential margin and intraoperative perforation of the tumour or bowel wall

- that monitoring of treatment standards and intervention towards departments not fulfilling acceptable standards may provide improved quality of treatment, and that the hospital caseload does predict outcome of rectal cancer surgery. Altogether, the national efforts launched ten years ago with education of surgeons and establishing a rectal cancer registry, have improved rectal cancer treatment in Norway.

## PERSPECTIVES

Current rectal cancer treatment in Norway is still facing challenges. Organisation of treatment, professional proficiency and hospital caseload may be crucial in order to improve preoperative assessment, surgical performance and the pathological examination. Therefore, surveillance of treatment standards must proceed, and failing quality has to be addressed.

The importance of optimal surgery for rectal cancer is now documented. Future research should focus on selection criteria for any adjuvant treatment in the context of optimal, quality-controlled, standardised surgery.

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# Paper III

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# Oncological outcomes after total mesorectal excision for cure for cancer of the lower rectum: anterior versus abdominoperineal resection

Arne Wibe, M.D.,* Astri Syse, M.Sc.,† Elisabeth Andersen, M.Sc.,† Steinar Tretli, M.Sc., Ph.D.,† Helge E. Myrvold, M.D., Ph.D.,* Odd Søreide, FRCS, FACS, ‡ on behalf of the Norwegian Rectal Cancer Group (see appendix)

*Department of Surgery, St. Olavs Hospital, Trondheim, †The Cancer Registry of Norway, ‡Centre for Health Technology Assessment, SINTEF Unimed, Oslo, Norway

From the Norwegian Gastrointestinal Cancer Group and the Norwegian Rectal Cancer Project.

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Address for correspondence and requests for reprints:

Arne Wibe, MD

Dept. of Surgery

St. Olavs Hospital, Trondheim

N-7006 Norway

Phone: + 47 73869161

Fax: + 47 73867428

E-mail: arne.wibe@medisin.ntnu.no

## Abstract

**Objective:** The object of this study is to examine the outcome of cancer of the lower rectum, particularly the rates of local recurrence and survival for tumors located in this area and that have been treated by anterior or abdominoperineal resections.

**Design:** A prospective observational national cohort study.

**Setting:** The study is part of the Norwegian Rectal Cancer Project. The present cohort includes all patients undergoing total mesorectal excision in 47 hospitals during the period November 1993–December 1999.

**Patients**: A total of 2136 patients with rectal cancer within 12 cm of the anal verge were analyzed; there were 1315 (62 percent) anterior resections (ARs) and 821 (38 percent) abdominoperineal resections (APRs). The lower edge of the tumor was located 0–5 cm from the anal verge in 791 patients, 6–8 cm in 558 patients and 9–12 cm in 787 patients. According to the TNM classification there were 33 percent stage I, 35 percent stage II and 32 percent stage III.

**Main outcome measures:** Five-year local recurrence and survival rates.

**Results:** *Univariate analyses:* The 5-year local recurrence rate was 15 percent in the lower level, 13 percent in the intermediate level and 9 percent in the upper level ($P = 0.014$). It was 10 percent local recurrence following AR and 15 percent following APR ($P = 0.008$). The 5-year survival rate was 59 percent in the lower level, 62 percent in the intermediate level and 69 percent in the upper level ($P < 0.001$), respectively, and it was 68 percent in the AR group and 55 percent in the APR group ($P < 0.001$). *Multivariate analyses:* The level of the tumor influenced the risk of local recurrence (HR = 1.8, 95 percent confidence interval (CI) = 1.1-2.3), but the operative procedure, AR vs. APR, did not (HR = 1.2, 95 percent CI = 0.7-1.8). On the contrary, operative procedure influenced survival (HR = 1.3, 95 percent CI = 1.0-1.6), but tumor level did not (HR = 1.1, 95 percent CI = 0.9-1.5). In addition to patient and tumor characteristics (T4 tumors), intraoperative bowel perforation and tumor involvement of the circumferential margin were identified as significant prognostic factors, which were more common in the lower rectum, explaining the inferior prognosis for tumors in this region.

**Conclusion:** T4 tumors, R1 resections and/or intraoperative perforation of the tumor or bowel wall are main features of low rectal cancers, causing inferior oncological outcomes for tumors in this area. If surgery is optimized, preventing intraoperative perforation and involvement of the CRM, the prognosis for cancers of the lower rectum seems not to be inherently different from that for tumors at higher levels. In that case, the level of the tumor or the type of resection will not be indicators for selecting patients for radiotherapy.

## Introduction

Over the last few decades, the treatment of cancer of the lower rectum has been characterized by an increased use of sphincter-saving procedures (i.e. anterior resections or AR). It is now possible to make a bowel anastomosis at literally any level in the pelvic region. These changes have been facilitated primarily by the introduction of stapling devices. Furthermore, better understanding of the biology of the cancer has changed practice, e.g. the '5-cm rule' for the distal margin of resection has been generally abandoned,[1-3] and many now accept any distal margin as long as the margin is tumor free.[4] Thus, the specific indications for an abdominoperineal resection (APR) have changed,[5] and there has been a focus on sphincter-saving surgery[5–10] and reconstructive modalities that may improve functional outcome following this procedure.[8, 11]

It has long been argued that outcome (local recurrence or LR and survival) is less favorable for tumors located in the lower rectum.[12–14] Many theories have been proposed to explain this phenomenon,[12, 15] and these have to some degree shaped treatment policies.

We still do not know whether it is the level of the tumor itself, or other factors, that lead to local failure. Surgeon-related factors are relevant, because there is a significant variability in outcome after rectal cancer resections.[16-20] In addition, the technical refinements exemplified by the introduction of mesorectal excision have significantly improved the results after rectal cancer surgery.[21] It is still not clear, however, whether the principle of mesorectal excision represents an advantage for patients undergoing APR.[15, 22]

The purpose of the present study is to evaluate the results of treatment of cancer of the lower rectum, also addressing the question of whether there are differences in outcome for those having AR against those having APR, using a large national cohort of patients undergoing mesorectal excision.

## Patients and methods

This study is part of the Norwegian Rectal Cancer Project,[23–25] which aims to improve rectal cancer treatment at a national level. Major elements of this initiative, which started in 1993, included standardization of surgery by educating surgeons in the principles of mesorectal excision, and standardized handling and reporting of the specimens according to Quirke's principles,[26] benchmarking the importance of the circumferential resection margin (CRM).[24] Data on every patient with rectal cancer in Norway are entered into the Norwegian Rectal Cancer Registry,[23] and each hospital receives reports about their own results compared to the national average.

The present cohort consists of 2136 patients with rectal cancer treated, with curative intent, by total mesorectal excision between November 1993 and December 1999. All patients had a tumor located between 0 and 12 cm from the anal verge and were undergoing AR or APR. Patients treated by Hartmann's procedure were not included, as the indications of this resection are based on clinical features different from the AR and the APR group (emergency surgery, older patients, comorbidity). As local recurrence and survival are main outcome measures, neither the R2 resections were included.

Clinical data were submitted on project-specific forms to the Rectal Cancer Registry located at the Cancer Registry of Norway. Data on histopathology were retrieved from the Registry's compulsory reporting system, and tumors were classified according to the TNM classification system.[27] Date of death was extracted from the Norwegian Cause of Death Registry.

Follow-up data were collected by routine reminders. The follow-up regimen adhered to the principles established by the Norwegian Gastrointestinal Cancer Group, which included clinical examination, proctoscopy, ultrasound of the liver, chest x-ray, and serum carcinoembryonic antigen. Commonly, follow-up consultations were undertaken every third month for 2 years, and thereafter every 6 months until 5 years. Follow-up was completed for all patients and the median follow-up time was 44 months (range 22–97 months).

Local recurrence (LR) rates are given as the sum of isolated LR and LR with concomitant distant metastases; survival rates denote overall (crude) survival.

**Analyses and statistical methods**

The patient, tumor and treatment characteristics are described using frequency tables according to tumor level and operative procedure (AR vs. APR) and were analyzed using $\chi^2$ statistics (Tables 1 and 2). The rates of LR and overall survival were analyzed by univariate statistical models (Kaplan–Meier and log-rank tests) (Tables 3 and 4). Time to occurrence of LR and death is given by stratified multivariate Cox regression analyses (Figs. 1–4). As it was the aim to consider differences of long time survival, the analyses do not include 60 (2.7 percent) patients who died within 30 days of the operation. Variations in the distribution of fragile patients (with cardiovascular disease or septic complications following surgery) might influence overall survival for the groups being studied.

The impact of potential prognostic factors for LR and survival is analyzed by multivariate Cox proportional hazard regression models. The regressions were performed backwards with a cutoff *P*-value of 0.15, and the final results were confirmed by a forward procedure. The identification of independent predictors was completed by univariate analyses.

Significant variables were included in the final model (Table 5), where the best prognostic group for each variable acts as reference, giving a hazard ratio (HR) >1 for those at more risk for LR or death. If one variable was significant in either of the analyses of LR or survival, it was incorporated into both models. Radiation was included, based on significant impact in the univariate analysis, although not fulfilling statistical significance ($P = 0.08$) in the final multivariate model. The analyses were performed using the Statistical Package for the Social Sciences program (SPSS, Chicago, Illinois, US).

## Results

### General results

In the 74-month inclusion period, 2136 patients were treated by a total mesorectal excision[23] for an adenocarcinoma located within 12 cm of the anal verge. The median age was 69 years (range 18–94 years), and there were 893 (42 percent) women and 1243 (58 percent) men. The tumor was located 0–5 cm from the anal verge in 791 (37 percent) patients, from 6 to 8 cm in 558 (26 percent) patients and from 9 to 12 cm in 787 (37 percent) patients; 1315 (62 percent) patients were treated by AR and 821 (38 percent) by APR.

Thirty-three percent (702) were stage I, 35 percent (748) stage II and 32 percent (686) stage III. Consequently 67 percent had a high-risk tumor (stage II and III); 190 patients (9 percent) had a T4 tumor.

Intraoperative perforation of the bowel wall occurred in 184 (9 percent) resections, and the CRM was involved (CRM ≤ 1 mm) by tumor in 163 (8 percent) patients. Radiotherapy was given to 214 patients (10 percent), 124 patients (6 percent) preoperatively and 90 patients (4 percent) postoperatively. Chemotherapy was not an integral part of the Norwegian treatment policy for rectal cancer during this period.[23]

### Characteristics related to tumor level

Table 1 gives the frequencies of patient and tumor characteristics related to the tumor level. Age distribution was similar for all tumor levels. The proportion of women with tumors in the lower level was higher (45 percent) than those with tumors in the intermediate (40 percent) and upper levels (39 percent) ($P = 0.034$).

T4 tumors were more frequent (13 percent) in the lower rectum than in the higher levels (6 percent and 7 percent) ($P < 0.001$), although the tumor diameter was similar at all levels (data not given). The N status did not differ according to tumor level, but at the highest level there were fewer stage I and more stage II tumors ($P = 0.032$) than in the lower and intermediate levels. Of the tumors in the lower level, 14 percent showed little differentiation, versus 10 percent and 7 percent in the intermediate and upper levels, respectively ($P = 0.001$).

Bowel or tumor perforation during resection occurred in 5 percent of the resections of the tumors at the highest level, 8 percent at the intermediate level and 13 percent at the lower level ($P < 0.001$).

Tumor involvement of the CRM was identified in 6 percent of cancers at the upper level, and in 5 percent and 11 percent at the intermediate and the lower levels, respectively ($P = 0.001$). Radiotherapy was used more often for distal tumors, preoperatively as well as postoperatively, and altogether, 15 percent of low-level tumors and 6 percent of high-level tumors were irradiated ($P < 0.001$).

**Characteristics related to type of resection**

Table 2 describes patient and treatment characteristics according to type of resection. The age distribution was significantly different in the AR group from that in the APR group. Younger patients (< 70 years) underwent AR more often, with older patients being more likely to undergo APR ($P = 0.001$). There were 14 percent T4 tumors in the APR group versus 6 percent in the AR group ($P < 0.001$). The distributions of N status and TNM stages were similar for APR and AR. Of the tumors in the APR group, 13 percent had little differentiation compared to 9 percent in the AR group ($P = 0.002$).

Intraoperative perforation of the tumor or bowel wall occurred in 16 percent of the APRs and 4 percent of the ARs ($P < 0.001$), and frequency of tumor involvement of the CRM was 12 percent following APR versus 5 percent following AR ($P < 0.001$).

Radiotherapy was more often used in the APR group than in the AR group, as 135 patients (16 percent) who underwent APR and 79 patients (6 percent) who underwent AR ($P < 0.001$) were given preoperative or postoperative radiotherapy.

**Local recurrence and survival**

The 5-year overall LR rate was 12 percent (95 percent confidence interval (CI) = 10-13). The local recurrence rate was 15 percent (95 percent CI = 12-18) in the lower level, 13 percent (95 percent CI = 9-16) in the intermediate level and 9 percent (95 percent CI = 7-11) in the upper level ($P = 0.014$) (Table 3). The LR rate after AR and APR was 10 percent (95 percent CI = 8-12) and 15 percent (95 percent CI = 12-18), respectively ($P = 0.008$) (Table 4).

The cumulative LR rate with time was similar in the lower and intermediate levels, but significantly less in the upper level (Figure 1). There was, however, no difference in LR rate according to resection type after adjusting for prognostic factors (Fig. 2 and Table 5). Fifty percent of the recurrences occurred within 19 months and 90 percent within 40 months.

The 5-year overall survival rate for the entire patient population was 63 percent (95 percent CI = 61-66); 69 percent (95 percent CI = 65-73) at the highest level, 62 percent (95 percent CI = 57-66) at the intermediate level, and 59 percent (95 percent CI = 55-63) at the lowest level ($P < 0.001$) (Table 3). The multivariate analyses, which adjusted for all significant variables, showed that the level of the tumor was close to be identified as an independent predictor of overall survival (*P* = 0.072*)* (Table 5, Fig. 3).

After AR and APR, the 5-year survival rate was 68 percent (95 percent CI = 66-71) and 55 percent (95 percent CI = 52-59), respectively (*P* < 0.001) (Table 4 and Fig. 4).

**Prognostic factors**

The multivariate analyses (Table 5) demonstrated that T and N status, tumor level, intraoperative perforation and involved CRM influenced LR rates, whereas resection type did not. Thus, for patients undergoing AR or APR, given an identical T and N status, tumor level, and frequency of perforation and margin involvement, the LR rates were not significantly different (Fig. 2).

T4 tumors increased the LR risk by a factor (HR) of 4.7 (95 percent CI = 1.9–11.7), and intraoperative perforation increased LR with an HR of 2.9 (95 percent CI = 2.0–4.2). The observed LR rate (44 months median follow-up) was 23 percent after perforation and 9 percent in the group who had no perforation.

Overall survival declined with increasing age; the mortality risk for those > 79 years was increased (HR = 6.1; 95 percent CI = 3.8–9.9) compared with those < 50 years (Table 5). Women survived better than men (HR = 1.4; 95 percent CI = 1.2–1.6). Tumor characteristics, such as T and N status and tumor differentiation, also influenced survival, and the HR for T4 tumors, compared to T1 tumors, was 3.6 (95 percent CI = 2.3–5.7).

The multivariate analysis revealed reduced survival at the intermediate level compared to the high level (HR = 1.3; 95 percent CI 1.0-1.6), but no difference between the high and the low tumor level (HR = 1.1; 95 percent CI = 0.9-1.5) (Table 5). Thus, the univariate analysis of survival (Table 3) showing better survival for tumors in the high level group than for those at the low level could be explained by less favorable patient, tumor and treatment related factors (i.e. intraoperative perforation and margin involvement) in the lower regions of the rectum, particularly in the group treated with APR (Tables 1 and 2).

Even though the type of resection did not influence the LR risk, there was a significantly better survival in the AR group. The risk of dying was increased by 30 percent (HR = 1.3; 95 percent CI = 1.0–1.6) among those who underwent APR compared to those having an AR. Intraoperative perforation of the bowel wall increased the mortality risk by 30 percent (HR = 1.3; 95 percent CI = 1.1–1.7), and tumor involvement of the CRM increased mortality with 40 percent (HR of 1.4; 95 percent CI = 1.1–1.8).

The 5-year survival rate was 31 percent (95 percent CI = 24–40) in the group with an involved CRM, and 66 percent (95 percent CI = 64–69) in the group with a noninvolved margin.

Radiotherapy was not identified as an outcome predictor in the multivariate analysis of local recurrence (HR = 1.4; 95 percent CI 0.9-2.2), neither of survival (HR = 1.3; 95 percent CI 1.0-1.6, *P* = 0.082).

## Discussion

It is a commonly held opinion – based on previous observational studies[12–14] – that cancers of the lower rectum have a less favorable oncological outcome than those at higher levels. A critical review of the literature does not, however, reveal any explicit cause for a possible inherent poor prognosis for low-level tumors.

Miles, who introduced APR in 1906, based his work on the notion that the spread of tumors of the lower rectum occurred towards the lymph nodes outside the levator ani muscles. APR was thought to deal with this problem. Later studies have not upheld Miles' concept.[15, 22]

A common problem in some studies that address this question is the lack of multivariate analyses that include main predictors in order to avoid confounding, especially the prognostic impact of intraoperative perforation and the involvement of the CRM.[12, 13, 15, 22]

Furthermore, the focus of the studies has not been exclusively related to data that could elucidate the potential effect of tumor level, e.g. APR has been claimed to be oncologically inferior to AR.[15] It was assumed that APR increased the risk of implantation of shed tumor cells, leading to more local recurrences than an AR. In our opinion, these arguments were not based on solid data; the study mentioned above was too small and firm conclusions cannot be drawn. In contrast, a much larger study, the Stockholm Rectal Cancer Study[28] ($n$ = 1292), could not identify any difference in LR rates after AR and APR (24 percent and 28 percent, respectively), in nonradiated patients, although mesorectal excision was not carried out in this series.

In addition, there is also a suspicion that many published studies are potentially biased (selection bias) because they present data from single centers with unclear referral practices.

The present study, which is based on a national cohort of patients treated in many hospitals over a contemporaneous period of time, gives a representative view of a population with rectal cancer and of treatment practice in routine care.

A significant characteristic of some seminal rectal cancer studies is the substantial variation in LR rates between hospitals and surgeons;[16–20] we know that surgical competence and skill determine outcome.[19, 29] Such data may support the assumption that the main problem with cancers in the lowest region may be related to technical proficiency. Therefore it could be presumed that routine use of radiotherapy for cancers of the lower rectum is a substitute for inferior surgical performance.

The data presented here support this view, because all patients received a standardized resection (mesorectal excision) and, in contrast to earlier reports,[12–14] the present study can identify no major difference (range 6 percent) in LR rates related to tumor level. Similarly, there was no difference in LR rates between AR and APR for comparable patient and tumor characteristics (Fig. 2). However, the survival rate was better for high-level tumors than it was for low-level tumors (Table 3), without tumor level being identified as a true predictor of survival (Table 5). Possibly this could be explained by less favorable patient, tumor and treatment factors in the lower regions of the rectum (Table 1).

This is illustrated by the fact that there were more T4 tumors in the lower levels of the rectum (13 percent versus 6 percent and 7 percent in the two higher levels – Table 1), and thus, more T4 tumors in the APR than the AR group (14 percent versus 6 percent – Table 2). Tumors with little differentiation were also more common at the low level compared to tumors of the high level (14 percent vs. 7 percent).

Radiotherapy was given to 214 patients (10 percent), most often as preoperative treatment of T4 tumors or postoperatively after intraoperative perforation of the bowel wall or tumor involvement of the CRM. Thus, radiotherapy was used more frequently for cancers of the lower rectum treated by APR (Tables 1 and 2), although in the present study radiotherapy had no independent prognostic impact on local recurrence.

Treatment-related factors also differed among tumor levels. Intraoperative perforation of the tumor or bowel wall was more common for tumors in the lower rectum being treated by an APR. We know that perforation of the bowel wall is a major cause of local recurrence;[30] this was verified by the multivariate regression analysis presented in Table 5, confirming the significance of the difference in LR rate between the group with and without perforation, (23 percent vs. 9 percent, respectively). The present data also showed that, the lower the tumor, the more often the CRM was involved by the tumor (Table 1). An involved CRM is followed by a significantly increased rate of LR and reduced survival[24] (Table 5). In this study the 5-year survival was 66 percent in the group with uninvolved CRM, compared to 31 percent in the group with involved CRM.

Thus, this study provides evidence that there are several independent factors with influence on outcome according to the level of the tumor. Frequency tables and univariate statistics describe the results at different levels, but they do not explain the cause of these differences. The present results demonstrate the importance of addition of multivariate statistical analyses to avoid confounding[31-33] in the search of independent outcome predictors which can guide treatment strategies.

In conclusion, the characteristics of the tumor, bowel perforation and involvement of the CRM are independent factors that significantly influence the outcome of cancer of the lower rectum. With regard to the LR rate, the level of the tumor is not a strong predictor, because this rate increases by only 6 percent from the highest to the lowest level. Furthermore, the type of resection does not influence the risk of LR.

As all the patient and tumor characteristics are fixed at the moment of diagnosis, including the level of the tumor, only the treatment-related factors can be influenced by the surgeon. The main message of the current data is, therefore, that intraoperative perforation and/or involved margin is to be avoided while operating on cancers of the lower rectum. If surgery is optimized, preventing intraoperative perforation and involvement of the CRM, the prognosis for cancers of the lower rectum seems not to be inherently different from that for tumors at higher levels. In that case, the level of the tumor or the type of resection will not be indicators for selecting patients for radiotherapy.

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# Appendix

**Steering Group:** The Norwegian Gastrointestinal Cancer Group

Chairman: Olav Dahl, Department of Oncology, Haukeland Hospital, Bergen.

**Project group members:** Tormod Bjerkeset, Innherred Hospital; Erik Carlsen, Ullevaal Hospital (chairman); Olav Dahl, Haukeland Hospital; Tor J. Eide, National Hospital; Trond Ellingsen, Harstad Hospital; Tore Gauperaa, Aust-Agder Central Hospital; Tom Gerner, Oppland Central Hospital Lillehammer; Øyvind Irtun, Tromsø University Hospital; Hartwig Kørner, Rogaland Central Hospital; Frøydis Langmark, Cancer Registry of Norway; Helge E. Myrvold, St. Olavs Hospital; Jarle Norstein, Cancer Registry of Norway; Arne Skarstein, Haukeland Hospital; Johan N. Wiig, Norwegian Radium Hospital.

## Participating hospitals and surgeons:

Aker Hospital (Arild Nesbakken, MD), Akershus Central Hospital (Arne E. Færden, MD), Aust-Agder Central Hospital (Tore Gauperaa, MD), Buskerud Central Hospital (Ulf Jacobsen, MD), Bærum Hospital (Rocio Rosales, MD), Diakonhjemmet Hospital (Jan H. Solhaug, MD), Diakonissehjemmets Hospital (Trond Haugstvedt, MD), Hedmark Central Hospital, Elverum (Øyvind Graadal, MD), Hedmark Central Hospital, Hamar (Øyvind Graadal, MD), Hammerfest Hospital (Svein Hammelbo, MD), Harstad Hospital (Trond Ellingsen, MD), Haugesund Hospital (Knut Svendby, MD), Haukeland Hospital (Arne Skarstein, MD), Innherred Hospital (Tormod Bjerkeset, MD), Kirkenes Hospital (Lennart Wählby, MD), Kongsvinger Hospital (Mikael Bech, MD), Kristiansund Hospital (Håkan Steen, MD), Larvik Hospital (Odd Ruistuen, MD), Lærdal Hospital (Fritjof Lund-Larsen, MD), Molde Hospital (Arve Sæbø, MD), Moss Hospital (Torgeir Løvig, MD), Møre og Romsdal Central Hospital (Sverrir Olafsson, MD), Namdal Hospital (Hallvard Græsli, MD), Nordland Central Hospital (Hans Wasmuth, MD), Oppland Central Hospital Gjøvik (Olav Høstmælingen, MD), Oppland Central Hospital, Lillehammer (Bjørn H. Nilsen, MD), Orkdal Sanitetsforenings Hospital (Bjørn G. Hansen, MD), Rana Hospital (Ranveig K. Aspevik, M.D.), The Norwegian Radium Hospital (Johan N. Wiig, MD), The National Hospital (Øystein Mathisen, MD), Ringerike Hospital (John Colin Poole, MD), Rjukan Hospital (Kjetil Unneberg, MD), Rogaland Central Hospital (Hartwig Kørner, MD), Sogn og Fjordane Central Hospital (Nils Sletteskog, MD), Stensby Hospital (Johan Lykke, MD), Stord Hospital (Olav Stray, MD), Stokmarknes Hospital (Rune Svensen, MD), Telemark Central Hospital (John Bjørn Nilsen, MD), Tromsø University Hospital (Øyvind Irtun, MD), St. Olavs Hospital (Helge E. Myrvold, MD), Ullevaal University Hospital (Erik Carlsen, MD), Vefsn Hospital (Øistein Ylvisaker, MD), Vest-Agder Central Hospital (Leif Ø. Heen, MD), Vestfold Central Hospital (Geir Haarberg, MD), Volda Hospital (Yngve Nordervald, MD), Voss Hospital (Hans Jørgen Nielsen, MD), Østfold Central Hospital (Thorleif E. Wilhelmsen, MD).

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Table 1 Distribution of Variables Related to Tumor Level

| Variables | Tumor Level (cm) 0-5 cm n | % | 6-8 cm n | % | 9-12 cm n | % | *P* |
|---|---|---|---|---|---|---|---|
| **Age group (yrs)** | | | | | | | 0.070 |
| < 50 | 52 | 7 | 25 | 4 | 54 | 7 | |
| 50-59 | 113 | 14 | 91 | 16 | 119 | 15 | |
| 60-69 | 190 | 24 | 172 | 31 | 225 | 29 | |
| 70-79 | 307 | 39 | 196 | 35 | 276 | 35 | |
| ≥ 80 | 129 | 16 | 74 | 13 | 113 | 14 | |
| **Sex** | | | | | | | 0.034 |
| Male | 432 | 55 | 333 | 60 | 478 | 61 | |
| Female | 359 | 45 | 225 | 40 | 309 | 39 | |
| **Type of resection** | | | | | | | < 0.001 |
| APR | 673 | 85 | 119 | 21 | 29 | 4 | |
| AR | 118 | 15 | 439 | 79 | 758 | 96 | |
| **Tumor status (T)** | | | | | | | < 0.001 |
| 1 | 84 | 11 | 57 | 10 | 78 | 10 | |
| 2 | 236 | 30 | 177 | 32 | 198 | 25 | |
| 3 | 369 | 47 | 289 | 52 | 458 | 58 | |
| 4 | 102 | 13 | 35 | 6 | 53 | 7 | |
| **Node status (N)** | | | | | | | 0.903 |
| 0 | 536 | 68 | 378 | 68 | 535 | 68 | |
| 1 | 182 | 23 | 125 | 22 | 174 | 22 | |
| 2 | 72 | 9 | 55 | 10 | 78 | 10 | |
| **TNM stage** | | | | | | | |
| I | 268 | 34 | 203 | 36 | 231 | 29 | 0.032 |
| II | 269 | 34 | 175 | 31 | 304 | 39 | |
| III | 254 | 32 | 180 | 32 | 252 | 32 | |
| **Differentiation** | | | | | | | 0.001 |
| High | 57 | 7 | 38 | 7 | 64 | 8 | |
| Moderate | 589 | 74 | 427 | 76 | 614 | 78 | |
| Low | 107 | 14 | 53 | 10 | 58 | 7 | |
| Missing | 38 | 5 | 40 | 7 | 51 | 6 | |
| **Perforation** | | | | | | | < 0.001 |
| Yes | 101 | 13 | 42 | 8 | 41 | 5 | |
| No | 690 | 87 | 516 | 92 | 746 | 95 | |
| **Involved CRM** * | | | | | | | 0.001 |
| Yes | 84 | 11 | 29 | 5 | 50 | 6 | |
| No | 707 | 89 | 529 | 95 | 737 | 94 | |
| **Adjuvant radiotherapy** | | | | | | | < 0.001 |
| Yes | 115 | 15 | 48 | 9 | 51 | 6 | |
| No | 676 | 85 | 510 | 91 | 736 | 94 | |

* CRM = circumferential resection margin

Table 2 Distribution of Variables Related to Type of Resection

| | Type of Resection | | | | |
|---|---|---|---|---|---|
| | APR | | AR | | *P* |
| **Variables** | n | % | n | % | |
| **Age group (yrs)** | | | | | 0.001 |
| < 50 | 50 | 6 | 81 | 6 | |
| 50-59 | 103 | 13 | 220 | 17 | |
| 60-69 | 203 | 25 | 384 | 29 | |
| 70-79 | 320 | 39 | 459 | 35 | |
| ≥ 80 | 145 | 18 | 171 | 13 | |
| **Sex** | | | | | 0.603 |
| Male | 472 | 57 | 771 | 59 | |
| Female | 349 | 43 | 544 | 41 | |
| **Tumor level (cm)** | | | | | |
| 0-5 cm | 673 | 82 | 118 | 9 | < 0.001 |
| 6-8 cm | 119 | 14 | 439 | 33 | |
| 9-12 cm | 29 | 4 | 758 | 58 | |
| **Tumor status (T)** | | | | | < 0.001 |
| 1 | 91 | 11 | 128 | 10 | |
| 2 | 240 | 29 | 371 | 28 | |
| 3 | 374 | 46 | 742 | 56 | |
| 4 | 116 | 14 | 74 | 6 | |
| **Node status (N)** | | | | | |
| 0 | 562 | 69 | 887 | 68 | 0.599 |
| 1 | 181 | 22 | 300 | 23 | |
| 2 | 77 | 9 | 128 | 10 | |
| **TNM stage** | | | | | 0.514 |
| I | 282 | 34 | 420 | 32 | |
| II | 281 | 34 | 467 | 36 | |
| III | 258 | 31 | 428 | 32 | |
| **Differentiation** | | | | | 0.002 |
| High | 70 | 9 | 89 | 7 | |
| Moderate | 597 | 73 | 1033 | 79 | |
| Low | 106 | 13 | 112 | 9 | |
| Missing | 48 | 6 | 81 | 6 | |
| **Perforation** | | | | | < 0.001 |
| Yes | 131 | 16 | 53 | 4 | |
| No | 690 | 84 | 1262 | 96 | |
| **Involved CRM *** | | | | | |
| Yes | 95 | 12 | 68 | 5 | < 0.001 |
| No | 726 | 88 | 1247 | 95 | |
| **Adjuvant radiotherapy** | | | | | < 0.001 |
| Yes | 135 | 16 | 79 | 6 | |
| No | 686 | 84 | 1236 | 94 | |

* CRM = circumferential resection margin

Table 3 5-year Local Recurrence and Overall Survival According to Tumor Level.

| **Tumor Level** | **No of Patients** | **Local Recurrence** | | | | **Survival** | | |
|---|---|---|---|---|---|---|---|---|
| | n | n | % | 95% CI* | *P*** = 0.014 | % | 95% CI* | *P***< 0.001 |
| 0-5 cm | 791 | 95 | 15 | 12-18 | | 59 | 55-63 | |
| 6-8 cm | 558 | 59 | 13 | 9-16 | | 62 | 57-66 | |
| 9-12 cm | 787 | 62 | 9 | 7-11 | | 69 | 65-73 | |
| Total | 2136 | 216 | 12 | 10-13 | | 63 | 61-66 | |

*Kaplan-Meier ** log rank test

Table 4 5-year Local Recurrence and Overall Survival According to Type of Resection.

| **Resection** | **No of Patients** | **Local Recurrence** | | | | **Survival** | | |
|---|---|---|---|---|---|---|---|---|
| | n | n | % | 95% CI* | *P*** = 0.008 | % | 95% CI* | *P***< 0.001 |
| AR | 1315 | 117 | 10 | 8-12 | | 68 | 66-71 | |
| APR | 821 | 99 | 15 | 12-18 | | 55 | 52-59 | |
| Total | 2136 | 216 | 12 | 10-13 | | 63 | 61-66 | |

*Kaplan-Meier ** log rank test

Table 5 Factors Influencing Local Recurrence and Survival in 2136 Patients with Rectal Cancer *

| | Local recurrence | | | Survival | | |
|---|---|---|---|---|---|---|
| **Variables** | **Hazard ratio** | **95% CI** | ***P*** | **Hazard ratio*** ** | **95% CI** | ***P*** |
| **Age group (yrs)** | | | | | | |
| < 50 | reference | | 0.338 | reference | | < 0.001 |
| 50-59 | 1.2 | 0.6-2.3 | | 1.2 | 0.7-2.1 | |
| 60-69 | 1.5 | 0.8-2.9 | | 1.9 | 1.2-3.1 | |
| 70-79 | 1.1 | 0.6-2.1 | | 3.1 | 1.9-5.0 | |
| ≥ 80 | 1.3 | 0.7-2.7 | | 6.1 | 3.8-9.9 | |
| **Sex** | | | | | | |
| Female | reference | | 0.37 | reference | | < 0.001 |
| Male | 1.1 | 0.9-1.5 | | 1.4 | 1.2-1.6 | |
| **Tumor level** | | | | | | |
| 9-12 cm | reference | | 0.027 | reference | | 0.072 |
| 6-8 cm | 1.6 | 1.1-2.9 | | 1.3 | 1.0-1.6 | |
| 0-5 cm | 1.8 | 1.1-2.3 | | 1.1 | 0.9-1.5 | |
| **Tumor status (T)** | | | | | | |
| 1 | reference | | < 0.001 | reference | | < 0.001 |
| 2 | 1.4 | 0.6-3.4 | | 1.2 | 0.8-1.9 | |
| 3 | 2.8 | 1.2-6.6 | | 2.4 | 1.6-3.6 | |
| 4 | 4.7 | 1.9-11.7 | | 3.6 | 2.3-5.7 | |
| **Node status (N)** | | | | | | |
| 0 | reference | | < 0.001 | reference | | < 0.001 |
| 1 | 1.9 | 1.4-2.7 | | 1.8 | 1.5-2.1 | |
| 2 | 2.4 | 1.6-3.6 | | 2.8 | 2.2-3.5 | |
| **Differentiation** | | | | | | |
| High | reference | | 0.876 | reference | | 0.001 |
| Medium | 1.0 | 0.5-1.7 | | 0.9 | 0.7-1.3 | |
| Low | 1.1 | 0.6-2.1 | | 1.5 | 1.0-2.1 | |
| **Resection type** | | | | | | |
| AR | reference | | 0.504 | reference | | 0.039 |
| APR | 1.2 | 0.7-1.8 | | 1.3 | 1.0-1.6 | |
| **Perforation** | | | | | | |
| No | reference | | < 0.001 | reference | | 0.017 |
| Yes | 2.9 | 2.0-4.2 | | 1.3 | 1.1-1.7 | |
| **Involved CRM** ** | | | | | | |
| No | reference | | 0.043 | reference | | 0.003 |
| Yes | 1.6 | 1.0-2.4 | | 1.4 | 1.1-1.8 | |
| **Radiation** | | | | | | |
| Yes | reference | | 0.176 | reference | | 0.082 |
| No | 1.4 | 0.9-2.2 | | 1.3 | 1.0-1.6 | |

*n = 178 with missing values excluded. ** CRM = circumferential resection margin
*** hazard ratio increased by reduced survival

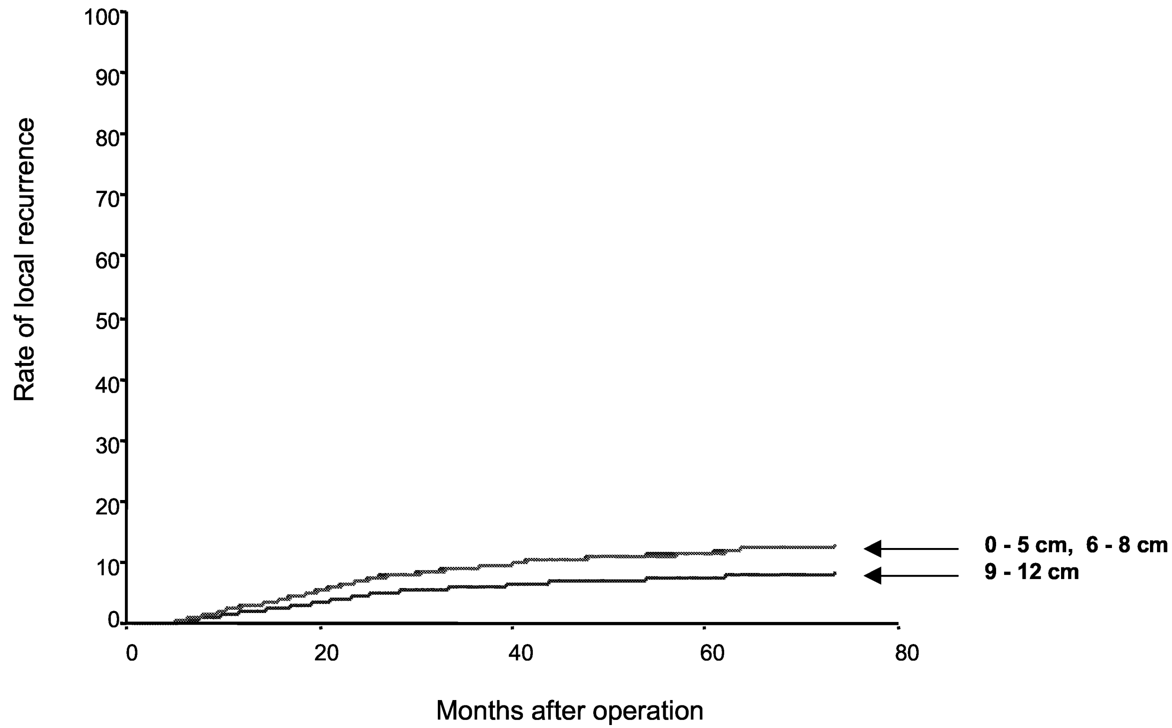
Legends

Figure 1 Local recurrence rates according to tumor level
(multivariate Cox regression analysis)

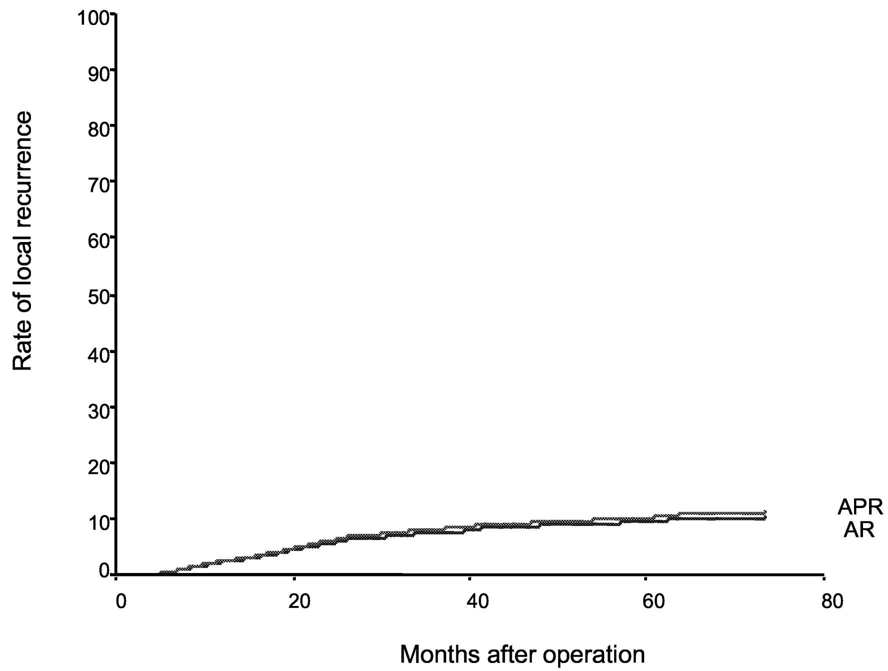
Figure 2 Local recurrence rates according to type of resection (AR vs. APR)
(multivariate Cox regression analysis)

Figure 3 Crude survival according to tumor level
(multivariate Cox regression analysis)

Figure 4 Crude survival according to type of resection (AR vs. APR)
(multivariate Cox regression analysis)

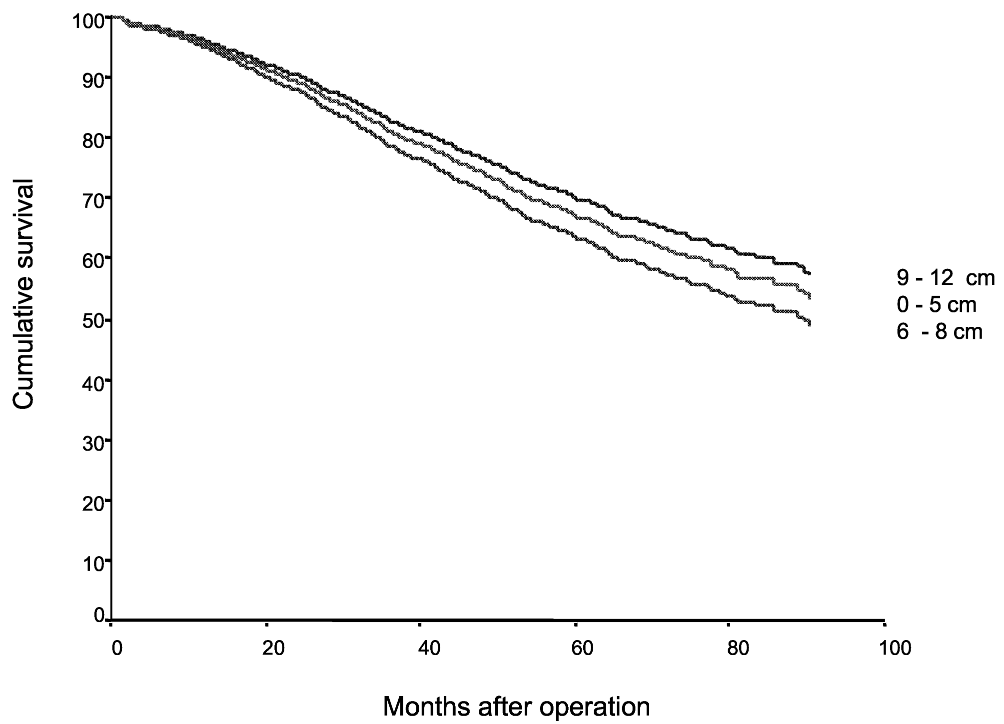



| | Numbers at risk | | | | |
|---|---|---|---|---|---|
| 9-12 cm | 787 | 678 | 445 | 238 | 91 |
| 6-8 cm | 558 | 468 | 304 | 155 | 68 |
| 0-5 cm | 791 | 657 | 389 | 206 | 80 |



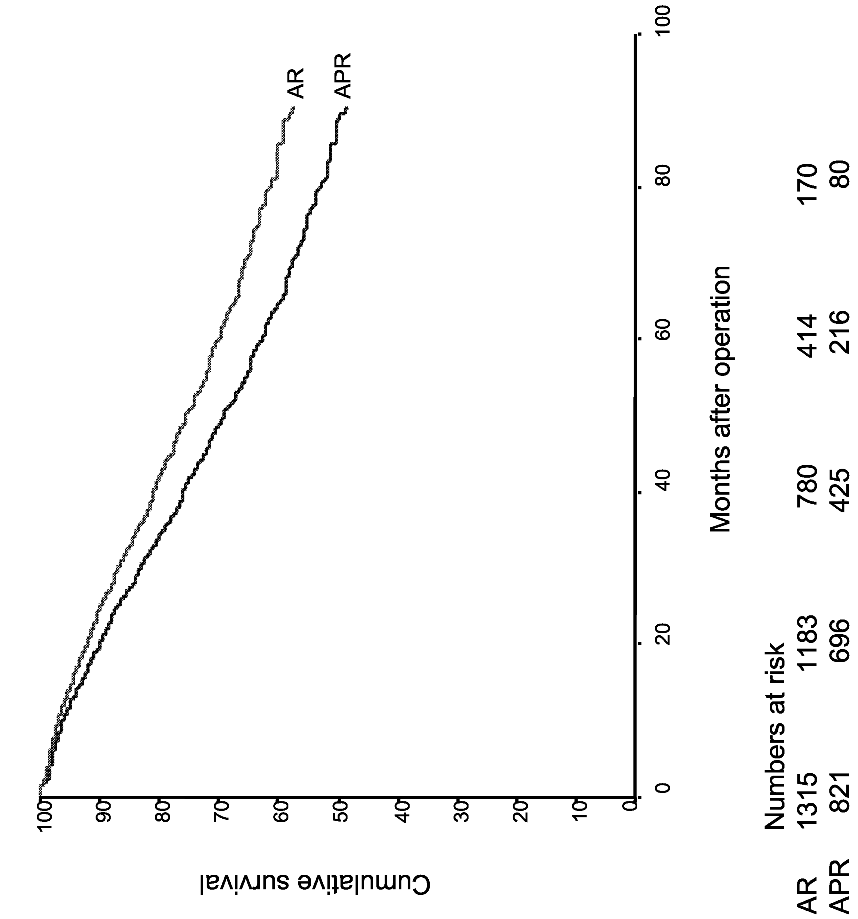

Numbers at risk

| | | | | | |
|---|---|---|---|---|---|
| AR | 1315 | 1130 | 742 | 396 | 164 |
| APR | 821 | 674 | 396 | 203 | 75 |




Numbers at risk

| | | | | | |
|---|---|---|---|---|---|
| 9-12 cm | 787 | 710 | 461 | 243 | 92 |
| 6-8 cm | 558 | 486 | 324 | 165 | 74 |
| 0-5 cm | 791 | 683 | 420 | 222 | 84 |


Cumulative survival
100
90
80
70
60
50
40
30
20
10
0
0
20
40
60
80
100
Months after operation
AR
APR
Numbers at risk
AR 1315 1183 780 414 170
APR 821 696 425 216 80

# Paper IV

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# Long-term outcome following standardisation of rectal cancer surgery on a national level - the effects of quality control and hospital caseload

Arne Wibe, Morten T. Eriksen[§], Astri Syse[†], Steinar Tretli[†], Harald Weedon-Fekjær[†], Erik Carlsen*, Olav Dahl[‡], Kjell M. Tveit*, Johan N. Wiig[#], Helge E. Myrvold, Odd Søreide[‡] on behalf of The Norwegian Rectal Cancer Group (see appendix)

Department of Surgery, St. Olavs Hospital, Trondheim, [§]Buskerud Hospital, Drammen, [†]The Cancer Registry of Norway, * Ullevaal University Hospital, Oslo, [‡] Haukeland University Hospital, Bergen, [#] The Norwegian Radium Hospital, Norway

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Address for correspondence and requests for reprints:
Arne Wibe, MD
Dept. of Surgery
St. Olavs Hospital, Trondheim
N-7006 Norway
Phone + 47 73869161
Fax + 47 73867428
E-mail arne.wibe@medisin.ntnu.no

There are no conflicts of interest.

**Summary**

**Background** The purpose of this study was to examine the influence of a rectal cancer registry as a quality control instrument of rectal cancer treatment on a national level. This prospective study also focuses on the rates of local recurrence and overall survival related to hospital caseload.

**Methods** As part of a national Rectal Cancer Project total mesorectal excision (TME) was implemented as the routine resection technique in Norway. A specific Rectal Cancer Registry was established to monitor treatment standards of single hospitals. This study includes all Norwegian patients with a rectal cancer within 15 cm from the anal verge treated for cure in the period November 1993 – December 1999.

**Findings** 3388 patients underwent an anterior resection, an abdominoperineal resection or a Hartmann's procedure. The hospitals were divided into four groups according to their annual caseload: Group 1 hospitals (n = 4) had ≥ 30 procedures, group 2 (n = 6) had 20-29 procedures, group 3 (n = 16) had 10-19 procedures and group 4 (n = 28) had < 10 procedures. From 1994 to 1999 the risk of local recurrence has decreased by 50% ($HR^{1999}$ = 0.5, 95% CI 0.4-0.8, p = 0.002). The five-year local recurrence rates were 9%, 15%, 13% and 18% in the four hospital caseload groups (p = 0.003), and five-year overall survival rates were 64%, 64%, 61% and 58% in the same four groups, respectively (p = 0.105). An annual hospital caseload less than ten increased the risk of local recurrence by 90% compared to hospitals with more than 30 procedures each year (HR = 1.9, 95% CI 1.3-2.7, p < 0.001).

The mortality risk was 20% higher for patients treated at hospitals with annual caseloads less than ten (HR = 1.2, 95% CI 1.0-1.5, p = 0.023).

**Interpretation** During the project, an improved quality of surgery measured as a lowered risk of local recurrence was demonstrated. The rate of local recurrence and the risk of mortality were higher at low caseload hospitals compared to hospitals with high treatment volumes (annual caseload <10 vs. ≥ 30).

## Introduction

Outcome after resection for rectal cancer has improved following standardisation of the surgical technique by introduction of total mesorectal excision (TME).[1-4] This technique has resulted in better local control and survival, not only in single, highly specialised units, but also on a population level (county and country).[4-6]

Still, there is a significant variation in outcome of rectal cancer surgery,[7, 8] and some authors report that hospital and surgeon caseload are significant predictors of postoperative morbidity, mortality and local recurrence.[8-10] Surgical training and technical skill may enhance the treatment of rectal cancer,[4, 11, 12] and specialisation of surgeons and a university hospital status appear to give better results compared to that of less specialised units.[10, 13]

The Norwegian Rectal Cancer Project has been running since November 1993.[1, 6, 14] A major element of this initiative was a comprehensive educational program to optimise treatment standards for rectal cancer in Norway. The purpose of this study was to examine the influence of a rectal cancer registry as a quality control instrument on a national level as well as for single departments treating rectal cancer. Main outcome measures were rates of postoperative mortality, anastomotic leakage, local recurrence (LR) and overall survival, particularly in relation to hospital caseload.

## Patients and methods

The Norwegian Rectal Cancer Project has been described in full.[1] In brief; it focused on surgical competence and skill, with standardisation of the technique of rectal resection. Training courses and "master classes" were arranged in different Health Regions in Norway, demonstrating the TME technique to the surgical community.

Pathologists were introduced to the principles of standardised handling and reporting of specimens, benchmarking slicing methods, with emphasis on tumour involvement of the circumferential resection margin (CRM).[15]

Based on professional consensus, it was recommended that a dedicated team of trained surgeons should handle all rectal cancer surgery. Major rectal resections were removed from the training curriculum of general surgeons and reserved for specialists in gastrointestinal surgery and those under training for this speciality. (GI-tract surgery is a recognised surgical speciality in Norway.)

A specific Rectal Cancer Registry enables the monitoring of outcome of rectal cancer treatment for single hospitals and at regional and national levels, and it provides feedback of results to each surgical department. Regular reports to single departments include their own results together with national averages for comparison. Departments with a potential flaw of quality have been supported, with theoretical and/or surgical assistance.

This Rectal Cancer Registry accumulates demographic and clinical data on project specific forms. Information on histopathology and staging are extracted from the pathology departments' obligatory reports to the Norwegian Cancer Registry. This dual reporting system provides the identification of rectal cancer patients on a population level. Routine reminders distributed to each surgical department obtaine follow-up information,[1] and dates of death are collected from Statistics Norway. Follow-up is complete for all patients and is facilitated by a unique 11-digit personal identification number.

This study included all 3388 patients with rectal cancer treated for cure in Norway (population 4.5 million) in the period November 1993 through December 1999 (Table 1). The tumours were located within 15 cm from the anal verge, and the patients were treated by an anterior resection (AR, n = 2164; 64%), an abdominoperineal resection (APR, n = 1010; 30%) or a Hartmann's procedure (n = 214; 6%). Rectal cancer surgery was performed at 54 hospitals, i.e. 34 local hospitals, 13 central hospitals (county level hospitals corresponds to District General Hospitals (UK)) and 7 university hospitals. The median number of patients treated in each hospital in the 74-month period was 46 (1-215). Four hospitals treated more than 180 patients, and 28 hospitals treated less than 60 patients.

The national policy of radiotherapy has been confined to selected high-risk groups. Preoperative radiotherapy (2 Gy x 25 or 5 Gy x 5) was recommended for T4 tumours, and postoperative chemoradiotherapy (2 Gy x 25 and concomitant bolus of

5-fluorouracil) was advised following intraoperative perforation of the tumour or bowel wall or if tumour involved the circumferential resection margin (CRM = 0-1 mm). Apart from this, neither radiotherapy nor chemotherapy has been recommended as an integrated part of rectal cancer treatment.

## Analyses and statistical methods

Patient, tumour and treatment characteristics and rates of anastomotic leakage and postoperative mortality according to different hospital caseload groups are described by frequency tabulations and analysed by $\chi^2$ statistics (Tables 1 and 2). The hospitals were divided into four groups according to their annual caseload: group 1 hospitals (n = 4) performed ≥ 30 major rectal resections each year, group 2 (n = 6) 20-29 resections, group 3 (n = 16) 10-19 resections and group 4 (n = 28) < 10 resections (Table 1).

LR rates (cumulative) are given as the sum of isolated LR (55%) and LR concomitant with distant metastases (45%). Survival rates denote overall (crude) survival.
The cumulative rates of LR and overall survival are given by Kaplan-Meier analyses (Tables 3 and 5, Figures 1, 2, 7, 8), and p-values were calculated by log rank tests. The postoperative mortality analyses of Table 2 considered the 106 patients who died within 30 days of the operation, and these patients were not included in the long-term survival analyses. A scatter plot describes the 5-year rates of LR related to the number of patients treated in each hospital during the study period (Figure 3). Figure 6 shows temporal analyses of LR rates of individual departments.

The impact of hospital caseload and of time of operation related to local recurrence rates were analysed by smooth Cox regression analyses using natural cubic splines with df = 3 and 4, in Figures 4 and 5, respectively.

Prognostic factors of LR and overall survival were analysed by multivariate Cox proportional hazard regression models (Table 4). The variables were analysed one by one, but adjusted for age, sex, T- and N-status, tumour level and grade (variables given at the time of diagnosis). An adjusted multivariate analysis, including hospital status and hospital caseload simultaneously, confirmed the independent prognostic impact of these two variables (data not shown).

Overall results were analysed and presented by dividing the national cohort into quartiles according to the rate of LR of individual hospitals (Table 5, Figures 7 and 8). As the quartile analyses use the same variable for analysis as the selection of quartile groups, it might be a problem of overestimating the differences due to the fact that hospitals with randomly low/high values would end up in the lower/higher quartiles. To quantify this problem, a simulation was done using the same hospital pattern, but giving an equal risk of local recurrence to each hospital. Performing 3000 simulations, it was observed a mean range of local recurrence of 8%-18%, showing that a considerable part of the differences of local recurrence and overall survival in Table 5 was real and not merely an effect of the analysis design.

The statistical analyses were performed by SPSS (Tables 1-5, Figures 1-3, 6- 8) and S-PLUS (Table 5, Figures 4 and 5).

## Results

Patient, tumour and treatment characteristics according to hospital caseload groups are presented in Table 1. The distribution of age, sex, T- and N-status and Dukes' stages were similar across the groups. Total mesorectal excision was used more often in large hospitals, i.e. in 90-95% of the patients, versus 69% in hospital group 4 (< 10 operations per year).

The postoperative mortality rate was not significantly increased in small hospitals compared to that of large hospitals (3.9% vs. 2.5%, p = 0.482). Similarly, anastomotic leakage did not seem to depend on hospital caseload, as it occurred less frequently in hospital group 1 and 4 compared to group 2 and 3; 8% in group 1 and 7% in group 4 versus 16% in group 2 and 11% in group 3 (p < 0.001; Table 2).

Large hospitals had lower rates of local recurrence and better survival than small hospitals. The cumulative five-year LR rates were 9%, 15%, 13% and 18% in the four hospital caseload groups respectively (p = 0.003, Table 3, Figure 1), and the five-year overall survival rates were 64%, 64%, 61% and 58% respectively (p = 0.105, Table 3, Figure 2).

Figure 3 describes the cumulative five-year LR rates of each hospital related to their total number of patients treated during the study period. This scatter plot has a triangular shape, which may suggest a relationship between hospital caseload and rate of LR.

This relationship is further explained by a smoothed splines regression (Figure 4), which indicates an effect of hospital caseload both at low and high volumes.

The risks of LR and death, adjusted for age, sex, T- and N-status, tumour level and tumour grade were explored by multivariate analyses (Table 4). Not performing a total mesorectal excision increased the risk of LR by 60% (hazard ratio (HR) = 1.6; 95% CI 1.2-2.1). An annual hospital caseload less than ten increased the risk of LR by 90% compared to hospitals performing more than 30 major resections yearly (HR = 1.9; 95% CI 1.3-2.7).

Hospital status influenced the risk of LR significantly with a 60% higher risk of LR for patients treated in local hospitals compared to university hospitals (HR = 1.6; 95% CI 1.2-2.2). However, there were no difference in LR between central hospitals and university hospitals (HR = 1.2; 95% CI 0.9-1.5).

Figure 5 demonstrates the learning effect of the national educational program, describing a continuously decreasing risk of local recurrence during the project ($p < 0.001$). The risk of LR has been significantly reduced since 1997, and in 1999 the risk of LR was 50% compared to that in 1994 ($HR^{1999} = 0.5$; 95% CI 0.4-0.8; Table 4).

The effect of monitoring treatment standards is given by Figure 6, showing LR rates of the five hospitals with the lowest LR rates in the period 1993-1996 compared to the five hospitals with the highest rates, and the evolution with time to the following period, 1997-1998. The hospitals with the lowest LR rates initially maintained, with one exception, their "good" results, whereas the five hospitals with the highest LR rates initially all improved with time.

Patients treated at high caseload hospitals had better survival than those treated at small volume hospitals. The risk of mortality was increased by 20% at hospitals with an annual caseload < 10 compared to patients treated at hospitals with caseload ≥ 30 (HR = 1.2; 95% CI 1.0-1.5). Patients treated at local hospitals had a survival similar to patients treated at university hospitals (Table 4). Thus, overall survival for rectal cancer patients did depend on hospital treatment volume, but formal hospital status seemed irrelevant.

The overall quality of major rectal cancer resections on a national level is illustrated by quartile analyses (Table 5, Figures 7 and 8). The five-year local recurrence rates were 7%, 10% and 13% respectively in the three best quartiles of the hospitals, compared to 22% in the fourth group. Five-year overall survival rates were 63% - 66% in the three best performing hospital quartiles, and 56% in the hospital quartile group with the highest local recurrence rate. These findings demonstrate the close association between LR and overall survival.

This national audit of rectal cancer treatment following implementation of TME cannot identify any benefit of radiotherapy (Table 4). Neither preoperative nor postoperative treatment seemed to reduce the risk of LR. Actually, preoperative radiotherapy implied reduced survival (HR (mortality risk) = 1.3, 95% CI 1.0-1.7).

## Discussion

The most important result of this study is the significant improvement of rectal cancer surgery after introduction of total mesorectal excision. Since the beginning of this project ten years ago, the single best parameter of surgical performance, the rate of local recurrence, has continuously declined. There is no doubt that introducing TME as the standard operative principle has improved the quality of surgery, but it has not entirely eliminated the problem of variation of results. Thus, it is still a potential for enhancing treatment standards.

One question we address here is how organizational factors potentially influence outcome, and how the care of these patients can be further optimised. The present data support the view that a quality control instrument (i.e. the Norwegian Rectal Cancer Project and Registry) can lead to a better outcome with time. The regular feedback of results to each surgical department implies a continuous focus on outcome of rectal cancer treatment, and departments not fulfilling acceptable treatment standards have been asked to address the problem.

This policy has worked. In the period 1994-1999 the LR rate has been reduced by 50% (Table 3), although with only a marginal effect on crude survival, so far. Hospitals with a quality problem during the first years of the project have been offered educational support, and they now have results comparable to the best group of hospitals (Figure 6). In addition, 15 low volume hospitals have on their own initiative stopped performing rectal cancer surgery, and the patients are now treated by fewer, more specialised surgeons in fewer hospitals.

We can conclude that ½ of the patient cohort has received optimised treatment with a risk of local recurrence at 5 years of $\leq$ 10%, and that another ¼ have been given acceptable rectal cancer care (Figures 7 and 8). This is a consequence of the introduction of mesorectal excision,[1-3] as radio- and/or chemotherapy has not been integrated parts of the routine treatment policy for rectal cancer during this period.

On the other hand, there is an obvious potential for improvement in the group of hospitals responsible for ¼ of the cohort. Improvement is a process, and the national Rectal Cancer Registry, postgraduate rectal cancer training courses assembling gastrointestinal surgeons, radiologists and pathologists, and the professional co-operation outlined earlier, are all factors contributing to good quality,[16] which will need to be continued.

We have previously argued that TME provides national results comparable to the results that have been reported following surgery combined with radiation and/or chemotherapy.[1, 14] As the need for adjuvant therapy will depend on the quality of surgery, and the current data suggest that training of surgeons and the focus on quality control are followed by a continuous decline of local recurrence, it may justify optimised surgery as the only treatment modality and using radiation and/or chemotherapy only selectively.[16] This study may not allow for any firm conclusion concerning adjuvant radiotherapy, as the statistical methods were not particularly designed to scrutinise that topic. However, the present data do not support the early results of the Dutch trial,[17] in which 1805 patients were randomised to TME with or without preoperative radiotherapy. It was reported a significant reduction of local recurrence in the group with adjuvant radiotherapy, although without any survival benefit. But, the median follow-up was only two years in the Dutch study, and as we know that radiotherapy can postpone local recurrence,[18] we should wait for the 5-year figures. Furthermore, that trial may not be comparable to the present study, as the Dutch cohort did not include patients with fixed tumours, neither patients with previous or coexisting cancer, nor those who had previously undergone large bowel surgery, chemotherapy or radiotherapy for any reason.

There are other important conclusions to be drawn from the present data. Hospital volume affects the rates of LR and survival; lower volumes increase the LR rate and reduce survival. Furthermore, good providers perform well, and vice versa, bad providers miss quality standards for various outcome measures (anastomotic leakage, postoperative mortality and LR, Tables 2-4). Finally, hospital status has an independent significant effect on outcome, as university hospitals perform better than local hospitals.

The relationship between hospital caseload and outcome of cancer care has been addressed in four important systematic reviews from the National Health Services Centre for Reviews and Dissemination (UK)[19, 20] and Institute of Medicine (IOM) (US).[21, 22] (A systematic review of the topic has also been published by The Norwegian Centre for Health Technology Assessment (SMM Report 2001:2; www.sintef.no/smm, in Norwegian)).

The overall conclusion of these reviews is that outcome after complex cancer operations are affected negatively by low volumes.

This relationship, however, is not so evident for colorectal cancer operations. The evidence table provided by the IOM report[22] showed that only 3 out of 5 studies fulfilling the inclusion criteria used in that report could demonstrate an effect of volume. The volume gradient for colorectal cancer operations was not marked with a difference in postoperative mortality between "high" and "low" volume providers of only one per cent.[22] The present results correspond well with the estimate given in the IOM report, as the present magnitude of the volume effect on postoperative mortality is relatively modest with an absolute difference of 1-2%. However, considering issues of long-term effects, i.e. LR and long- term survival, we will put forward as a postulate that a volume-outcome relationship after major rectal cancer surgery may have been cancelled out if rectal resections are grouped together with less complex colon resections.

The outcome measures in most of the studies published so far have been postoperative mortality and morbidity, but with a paucity of information on colorectal specific complications (anastomotic leak, intraabdominal abscesses, wound infection and genitourinary dysfunction), LR and long time survival. In the current study we have included rates of postoperative mortality, anastomotic leaks, cumulative LR and overall survival and report figures for these endpoints for major rectal cancer operations only. The conclusion is clear, low volumes have a detrimental effect.

In a Canadian study the rate of local recurrence was 10% among surgeons with “high” treatment volumes, compared to 21% for “low-volume” surgeons.[23] This appears to fit well with our data; the LR rate was doubled among patients treated in “low-volume” hospitals compared to that of patients treated in “high” volume hospitals (18% vs. 9%) (Figure 1, Tables 3 and 4). Here we have to bear in mind that the unit of analysis in the Canadian study was surgeons, while it was hospitals (or more correct surgical departments) in the current study. Others have concluded that surgeon-specific experience is the most sensitive unit of volume for the prediction of long-term survival.[24]

One problem is the variation in the definition of “low volume”. For instance, in the three studies in the IOM report,[22] “low volume hospitals” varied between less than 40 to less than 80 operations per year. In that respect, the majority of Norwegian hospitals will be low volume institutions. Clearly, as this and other of our papers show, most Norwegian hospitals operate with very low LR rates and high survival even with volumes that in other papers are categorised as low volume institutions.[1, 6, 14]

It is unclear where a threshold exists along the volume continuum, above which outcomes do not continue to improve with further volume increases. An interpretation of the present multivariate analyses indicates that the more often you perform rectal cancer surgery, the lower the risk of local recurrence (Figure 4). A large hospital caseload, however, is not a necessary part, nor a guarantee, for optimal outcome. There are hospitals with large caseloads with high LR rates, and vice versa, some hospitals with small or medium caseloads have low recurrence rates (Figure 3).

Thus, as "high" volume does not guarantee good results, the conclusion is that monitoring and auditing results – not as an ad hoc exercise, but as a routine – is a fundamental requisite for quality assurance (Figures 5 and 6), and such monitoring must allow for meaningful analyses of results. Consequently, volume is recognised as an imperfect, but easy to use and understand, correlate of quality, and volume per se does not result in good outcome.

The volume effect seems to be a proxy measure of other factors that affect care. The Institute of Medicine (2000) [23] has conceptualised the "volume" term and advanced the idea that the apparent volume-outcome relationship is better explained by health care structures and processes of care. Thus, surgeon skill and competence is not enough, for complex procedures skills of other clinicians and the hospital or organisational skill are equally important.[23, 25]

We believe that the superior results in university hospitals compared to local hospitals can be attributed to the phenomenon of collective skill and surgeons working in teams. Some may argue that our findings are an indirect evidence of the effect of subspecialisation or a more specific training in colorectal surgery. This is very hard to prove, particularly in the light of the individual surgeon volume effect demonstrated by some authors.[23, 26] We will argue that our data (Figure 3) show that the larger the caseload the lesser the variation in results. Furthermore, it is likely that a sustained focus on the quality of rectal cancer surgery is easier in an environment where more than one dedicated surgeon as well as other specialists concentrate to a large extent on colorectal cancer surgery only, compared to a department where single surgeons – although being trained and dedicated – is working more in isolation.

In conclusion, this study provides evidence that rectal cancer treatment can be improved by increasing hospital caseload, by increased organisational focus on rectal cancer treatment and by establishing a rectal cancer registry monitoring treatment standards throughout the country. National efforts to introduce total mesorectal excision as the preferred method have optimised rectal cancer treatment in most hospitals, but there is a potential for further improvement for hospitals treating one fourth of the patients.

### Contributors

Members of the Norwegian Rectal Cancer Group, listed in the appendix, initiated the project and participated in the education of Norwegian surgeons. The data were collected by surgeons at 54 hospitals (see appendix). Statistical analyses were performed by A Wibe, A Syse, S Tretli and H Weedon-Fekjær. All authors have participated in designing the study, interpreting the data and preparing the report.

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## Appendix

Steering Group: The Norwegian Gastrointestinal Cancer Group

Chairman: Olav Dahl, Department of Oncology, Haukeland University Hospital, Bergen.

Project group members: Tormod Bjerkeset, Levanger Hospital; Erik Carlsen, Ullevaal University Hospital (chairman); Olav Dahl, Haukeland University Hospital; Tor J. Eide, Rikshospitalet University Hospital; Trond Ellingsen, Hålogaland Hospital Harstad; Tore Gauperaa, Aust-Agder Hospital; Tom Gerner, Oppland Central Hospital Lillehammer; Øyvind Irtun, University Hospital North Norway; Hartwig Kørner, Central Hospital of Stavanger; Frøydis Langmark, The Cancer Registry of Norway; Helge E. Myrvold, St. Olavs Hospital; Jarle Norstein, The Cancer Registry of Norway; Arne Skarstein, Haukeland University Hospital; Johan N. Wiig, The Norwegian Radium Hospital.

Participating hospitals and surgeons:

Aker University Hospital (Arild Nesbakken, MD), Akershus University Hospital (Arne E. Færden, MD), Aust-Agder Hospital (Tore Gauperaa, MD), Buskerud Hospital (Ulf Jacobsen, MD), Bærum Hospital (Rocio Rosales, MD), Central Hospital of Hedmark Elverum (Øyvind Graadal, MD), Central Hospital of Hedmark Hamar (Øyvind Graadal, MD), Central Hospital of Stavanger (Hartwig Kørner, MD), Diakonhjemmet Hospital (Jan H. Solhaug, MD), Førde Hospital (Nils Sletteskog, MD), Hammerfest Hospital (Svein Hammelbo, MD), Haraldsplass Diakonale Hospital (Trond Haugstvedt, MD), Haugesund Hospital (Knut Svendby, MD), Haukeland University Hospital (Arne Skarstein, MD), Helgeland Hospital Mo i Rana (Ranveig K. Aspevik, M.D.), Helgeland Hospital Mosjøen (Øistein Ylvisaker, MD), Helgeland Hospital Sandnessjøen (John Kufås, MD), Hålogaland Hospital Harstad (Trond Ellingsen, MD), Hålogaland Hospital Narvik (Ole E. Gabrielsen, MD), Hålogaland Hospital Stokmarknes (Rune Svensen, MD), Kirkenes Hospital (Lennart Wählby, MD), Kongsberg Hospital (Fredrik Kylberg, MD), Kongsvinger Hospital (Mikael Bech, MD), Kristiansund Hospital (Håkan Steen, MD), Levanger Hospital (Tormod Bjerkeset, MD), Lofoten Hospital, Lærdal Hospital

(Fritjof Lund-Larsen, MD), Molde County Hospital (Arve Sæbø, MD), Namsos Hospital (Hallvard Græsli, MD), Nordfjord Hospital, Nordland Central Hospital (Hans Wasmuth, MD), Notodden Hospital, Odda Hospital, Oppland Central Hospital Gjøvik (Olav Høstmælingen, MD), Oppland Central Hospital Lillehammer (Bjørn H. Nilsen, MD), Orkdal Sanitetsforenings Hospital (Bjørn G. Hansen, MD), Rikshospitalet University Hospital (Øystein Mathisen, MD), Ringerike Hospital HS (John Colin Poole, MD), Rjukan Hospital (Kjetil Unneberg, MD), St. Olavs Hospital (Helge E. Myrvold, MD), Stensby Hospital (Johan Lykke, MD), Stord Hospital (Olav Stray, MD), Telemark Hospital (John Bjørn Nilsen, MD), The Norwegian Radium Hospital (Johan N. Wiig, MD), Ullevaal University Hospital (Erik Carlsen, MD), University Hospital North Norway (Øyvind Irtun, MD), Vest-Agder Hospital (Leif Ø. Heen, MD), Vestfold County Hospital (Geir Haarberg, MD), Vestfold County Hospital Larvik (Odd Ruistuen, MD), Volda Hospital (Yngve Nordervald, MD), Voss Hospital (Hans Jørgen Nielsen, MD), Østfold Hospital Fredrikstad (Thorleif E. Wilhelmsen, MD), Østfold Hospital Moss (Torgeir Løvig, MD), Ålesund Hospital (Sverrir Olafsson, MD).

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Table 1. Characteristics of 3388 patients according to different hospital caseload groups.

| | | | Hospital caseload groups | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1 | | 2 | | 3 | | 4 | | |
| | Total | | >= 30 | | 20 - 29 | | 10 - 19 | | < 10 | | |
| No of hospitals | 54 | | 4 | | 6 | | 16 | | 28 | | |
| No of patients | 3388 | | 774 | | 854 | | 1352 | | 408 | | |
| | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | p value* |
| **Age group** (yrs) | | | | | | | | | | | 0.508 |
| < 60 | 644 | (20) | 152 | (20) | 176 | (21) | 244 | (18) | 72 | (18) | |
| 60 - 69 | 911 | (27) | 209 | (27) | 241 | (28) | 350 | (26) | 111 | (27) | |
| 70 - 79 | 1250 | (37) | 282 | (36) | 293 | (34) | 529 | (39) | 146 | (36) | |
| >= 80 | 583 | (16) | 131 | (17) | 144 | (17) | 229 | (17) | 79 | (19) | |
| **Sex** | | | | | | | | | | | 0.160 |
| Male | 1960 | (58) | 433 | (56) | 477 | (56) | 811 | (60) | 239 | (59) | |
| Female | 1428 | (42) | 341 | (44) | 377 | (44) | 541 | (40) | 169 | (41) | |
| **T** | | | | | | | | | | | 0.049 |
| 1 | 310 | (9) | 76 | (10) | 75 | (9) | 127 | (9) | 32 | (8) | |
| 2 | 880 | (26) | 217 | (28) | 228 | (27) | 333 | (25) | 102 | (25) | |
| 3 | 1867 | (55) | 416 | (54) | 481 | (56) | 730 | (54) | 240 | (59) | |
| 4 | 331 | (10) | 70 | (8) | 70 | (8) | 162 | (12) | 34 | (8) | |
| **N** | | | | | | | | | | | 0.381 |
| 0 | 2261 | (67) | 527 | (68) | 579 | (68) | 893 | (66) | 262 | (64) | |
| 1 | 799 | (24) | 172 | (22) | 207 | (24) | 322 | (24) | 98 | (24) | |
| 2 | 328 | (10) | 75 | (10) | 68 | (8) | 137 | (10) | 48 | (12) | |
| **Dukes** | | | | | | | | | | | 0.321 |
| A | 999 | (30) | 250 | (32) | 261 | (31) | 381 | (28) | 107 | (26) | |
| B | 1262 | (37) | 277 | (36) | 318 | (37) | 512 | (38) | 155 | (38) | |
| C | 1127 | (33) | 247 | (33) | 275 | (32) | 495 | (34) | 146 | (36) | |
| **Grade** | | | | | | | | | | | 0.002 |
| High | 267 | (8) | 57 | (8) | 46 | (6) | 137 | (11) | 27 | (7) | |
| Moderate | 2567 | (81) | 593 | (82) | 669 | (85) | 982 | (78) | 323 | (84) | |
| Low | 327 | (10) | 78 | (11) | 75 | (10) | 138 | (11) | 36 | (9) | |
| Missing | 227 | | | | | | | | | | |
| **Tumour level**** | | | | | | | | | | | 0.005 |
| 11 - 15 | 1050 | (32) | 257 | (34) | 250 | (30) | 386 | (29) | 157 | (39) | |
| 6 - 10 | 1309 | (39) | 278 | (36) | 346 | (41) | 547 | (42) | 138 | (34) | |
| 0 - 5 | 966 | (29) | 227 | (30) | 250 | (30) | 380 | (29) | 109 | (27) | |
| Missing | 63 | | | | | | | | | | |
| **Resection type** | | | | | | | | | | | < 0.001 |
| AR | 2164 | (64) | 516 | (67) | 547 | (64) | 840 | (62) | 261 | (64) | |
| APR | 1010 | (30) | 230 | (30) | 229 | (27) | 417 | (31) | 134 | (33) | |
| Hartmann | 214 | (6) | 28 | (4) | 78 | (9) | 95 | (7) | 13 | (3) | |
| **TME** | | | | | | | | | | | < 0.001 |
| Yes | 3014 | (90) | 733 | (95) | 808 | (95) | 1199 | (90) | 274 | (69) | |
| No | 342 | (10) | 37 | (5) | 39 | (5) | 140 | (11) | 126 | (32) | |
| Missing | 32 | | | | | | | | | | |
| **Perforation** | | | | | | | | | | | 0.341 |
| Yes | 307 | (9) | 65 | (8) | 86 | (10) | 113 | (8) | 43 | (11) | |
| No | 3080 | (91) | 709 | (92) | 768 | (90) | 1238 | (92) | 365 | (90) | |
| Missing | 1 | | | | | | | | | | |
| **CRM involved** *** | | | | | | | | | | | 0.033 |
| Yes | 293 | (9) | 60 | (8) | 60 | (7) | 140 | (10) | 33 | (8) | |
| No | 3085 | (91) | 713 | (92) | 789 | (93) | 1208 | (90) | 375 | (92) | |
| Missing | 10 | | | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Preop. radiotherapy** | | | | | | | | | | | < 0.001 |
| Yes | 176 | (5) | 45 | (6) | 16 | (2) | 109 | (8) | 6 | (2) | |
| No | 3212 | (95) | 729 | (94) | 838 | (98) | 1243 | (92) | 402 | (99) | |
| **Postop. radiotherapy** | | | | | | | | | | | 0.038 |
| Yes | 161 | (5) | 26 | (3) | 54 | (6) | 60 | (4) | 21 | (5) | |
| No | 3227 | (95) | 748 | (97) | 800 | (94) | 1292 | (96) | 371 | (95) | |
| **Radiotherapy (pre- or post-)** | | | | | | | | | | | < 0.001 |
| Yes | 330 | (10) | 67 | (9) | 70 | (8) | 166 | (12) | 27 | (7) | |
| No | 3058 | (90) | 707 | (91) | 784 | (92) | 1186 | (88) | 381 | (93) | |

* $\chi^2$ statistics

** Distance in centimeters from anal verge

*** CRM = Circumferential resection margin

Table 2. Rates of postoperative mortality and anastomotic leakage related to hospital caseload groups

| Annual | No of | Postoperative mortality | | | p* | Anastomotic leakage | | | p* |
|---|---|---|---|---|---|---|---|---|---|
| caseload | hospitals | No of pts. | No of deaths | % | 0.482 | No of AR | No of leaks | % | < 0.001 |
| >= 30 | 4 | 774 | 19 | 2.5 | | 516 | 43 | 8 | |
| 20 - 29 | 6 | 854 | 30 | 3.5 | | 547 | 85 | 16 | |
| 10 - 19 | 16 | 1352 | 41 | 3.0 | | 840 | 90 | 11 | |
| < 10 | 28 | 408 | 16 | 3.9 | | 261 | 19 | 7 | |
| Total | 54 | 3388 | 106 | 3.1 | | 2164 | 237 | 11 | |

* $\chi 2$ statistics

Table 3. Five year cumulative local recurrence rates and overall survival for different hospital casleoad groups (n = 3388)

| Annual caseload | No of hospitals | No of patients | **Local recurrence** % | 95% CI | p* 0.003 | No of patients | **Survival** % | 95% CI | p* 0.105 |
|---|---|---|---|---|---|---|---|---|---|
| >= 30 | 4 | 774 | 9 | 6.9-11.5 | | 755 | 64 | 60.8-68.0 | |
| 20 - 29 | 6 | 854 | 15 | 11.9-17.5 | | 824 | 64 | 60.6-67.4 | |
| 10 - 19 | 16 | 1352 | 13 | 10.5-14.5 | | 1311 | 61 | 58.0-63.6 | |
| < 10 | 28 | 408 | 18 | 13.2-21.8 | | 392 | 58 | 52.7-62.9 | |

* log-rank test

Table 4. Risk factors of local recurrence and mortality in 3325 patients with rectal cancer *

| | Local recurrence | | | Mortality | | |
|---|---|---|---|---|---|---|
| Variables** | Hazard ratio | 95% CI | p value | Hazard ratio | 95% CI | p value |
| **Resection type** | | | 0.534 | | | < 0.001 |
| AR | 1.0 | | | 1.0 | | |
| APR | 1.1 | 0.8-1.6 | 0.470 | 1.4 | 1.2-1.7 | < 0.001 |
| Hartmann | 0.8 | 0.5-1.4 | 0.485 | 1.5 | 1.2-1.8 | < 0.001 |
| **TME** | | | 0.002 | | | 0.514 |
| Yes | 1.0 | | | 1.0 | | |
| No | 1.6 | 1.2-2.1 | | 1.1 | 0.9-1.2 | |
| **Hospital caseload** | | | 0.002 | | | 0.099 |
| >= 30 | 1.0 | | | 1.0 | | |
| 20 - 29 | 1.6 | 1.2-2.2 | 0.004 | 1.1 | 1.0-1.3 | 0.178 |
| 10 - 19 | 1.3 | 0.9-1.7 | 0.140 | 1.0 | 0.9-1.2 | 0.613 |
| < 10 | 1.9 | 1.3-2.7 | < 0.001 | 1.2 | 1.0-1.5 | 0.023 |
| **Hospital status*** ** | | | 0.002 | | | 0.367 |
| University | 1.0 | | | 1.0 | | |
| Central | 1.2 | 0.9-1.5 | 0.321 | 1.0 | 0.8-1.1 | 0.558 |
| Local | 1.6 | 1.2-2.2 | 0.001 | 1.1 | 0.9-1.2 | 0.499 |
| **Year operated** | | | 0.015 | | | 0.017 |
| 1994 | 1.0 | | | 1.0 | | |
| 1995 | 0.7 | 0.5-1.0 | 0.073 | 1.0 | 0.9-1.2 | 0.588 |
| 1996 | 0.8 | 0.6-1.1 | 0.113 | 0.9 | 0.7-1.1 | 0.228 |
| 1997 | 0.6 | 0.4-0.8 | 0.003 | 1.0 | 0.9-1.3 | 0.654 |
| 1998 | 0.7 | 0.5-1.0 | 0.036 | 0.8 | 0.6-1.0 | 0.014 |
| 1999 | 0.5 | 0.4-0.8 | 0.002 | 0.9 | 0.7-1.1 | 0.14 |
| **Perforation** | | | < 0.001 | | | < 0.001 |
| No | 1.0 | | | 1.0 | | |
| Yes | 2.4 | 1.8-3.1 | | 1.4 | 1.2-1.7 | |
| **Involved CRM**** ** | | | 0.007 | | | < 0.001 |
| No | 1.0 | | | 1.0 | | |
| Yes | 1.5 | 1.1-2.1 | | 1.4 | 1.2-1.6 | |
| **Preop. radiotherapy** | | | 0.843 | | | 0.032 |
| No | 1.0 | | | 1.0 | | |
| Yes | 1.0 | 0.6-1.5 | | 1.3 | 1.0-1.7 | |
| **Postop. radiotherapy** | | | 0.537 | | | 0.374 |
| No | 1.0 | | | 1.0 | | |
| Yes | 0.9 | 0.6-1.3 | | 1.1 | 0.9-1.4 | |
| **Radiotherapy (pre- or post-)** | | | 0.681 | | | 0.017 |
| No | 1.0 | | | 1.0 | | |
| Yes | 0.9 | 0.7-1.3 | | 1.2 | 1.0-1.5 | |

* n = 63 excluded in the analyses because of missing values in one of the variables adjusted for.
** Adjusted for age, sex, T-status, N-status, tumour level and grade. *** n = 3259
**** CRM = circumferential resection margin

Table 5. Cumulative local recurrence and overall survival according to hospital quartile groups*

| Hospital quartile group | No of hospitals | No of patients | **5-year local recurrence** (%) | No of patients | **5-year overall survival** (%) |
|---|---|---|---|---|---|
| I | 17 | 858 | 7 | 833 | 66 |
| II | 9 | 817 | 10 | 795 | 63 |
| III | 7 | 878 | 13 | 853 | 63 |
| IV | 20 | 833 | 22 | 799 | 56 |

***** One hospital missing (n = 2) because the patients had too short follow-up

**Legends**

Figure 1 The risk of local recurrence related to hospital caseload groups. N = 3388. Kaplan-Meier analysis. Log rank p = 0.003.

Figure 2 Overall survival related to hospital caseload groups. N = 3282. Kaplan-Meier analysis. Log rank p = 0.105.

Figure 3 The five-year rates of local recurrence at each hospital related to hospital caseload for the period 11/93 – 12/99. (3 hospitals with LR = 100 percent (caseload: 1, 1 and 3) and 3 hospitals with follow-up < 60 months (caseload: 2, 2 and 6) not included).

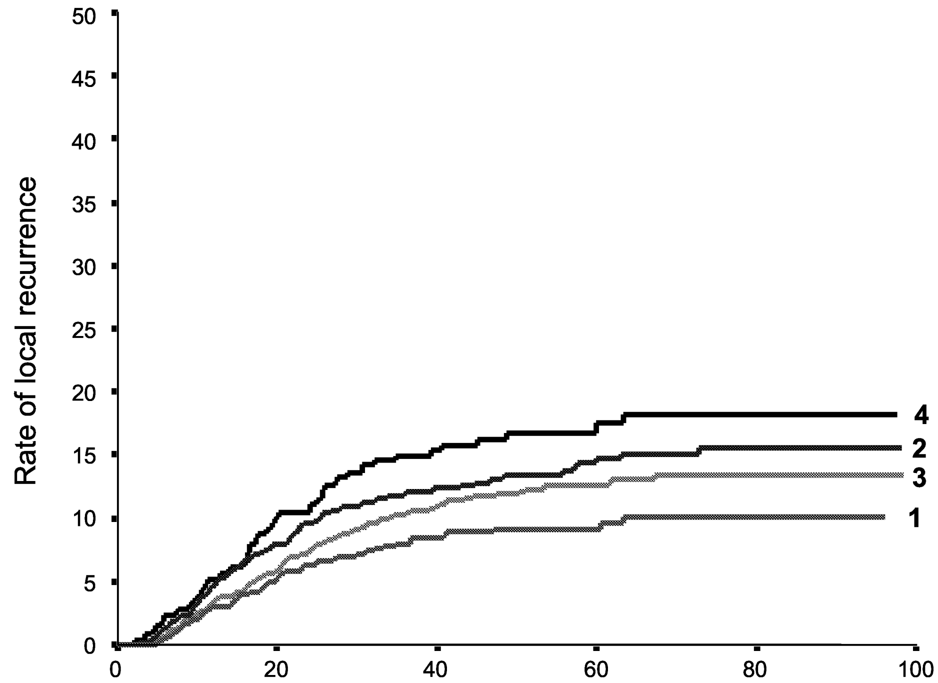
Figure 4 The risk of local recurrence related to hospital caseload estimated by smooth Cox regression analysis using natural cubic splines with df = 3.

Figure 5 The overall learning effect of the project expressed as the risk of local recurrence related to time of operation. Estimated by smooth Cox regression analysis using natural cubic splines with df = 4. Green lines give 95 percent point wise confidence intervals, p < 0.001.

Figure 6 The five-year local recurrence rates of the five “best hospitals” and the five “worst hospitals” in the period 1993-96 at the left. At the right, the rate of local recurrence for the same hospitals in the period 1997-98. Bold black line gives the national averages of the same two periods.

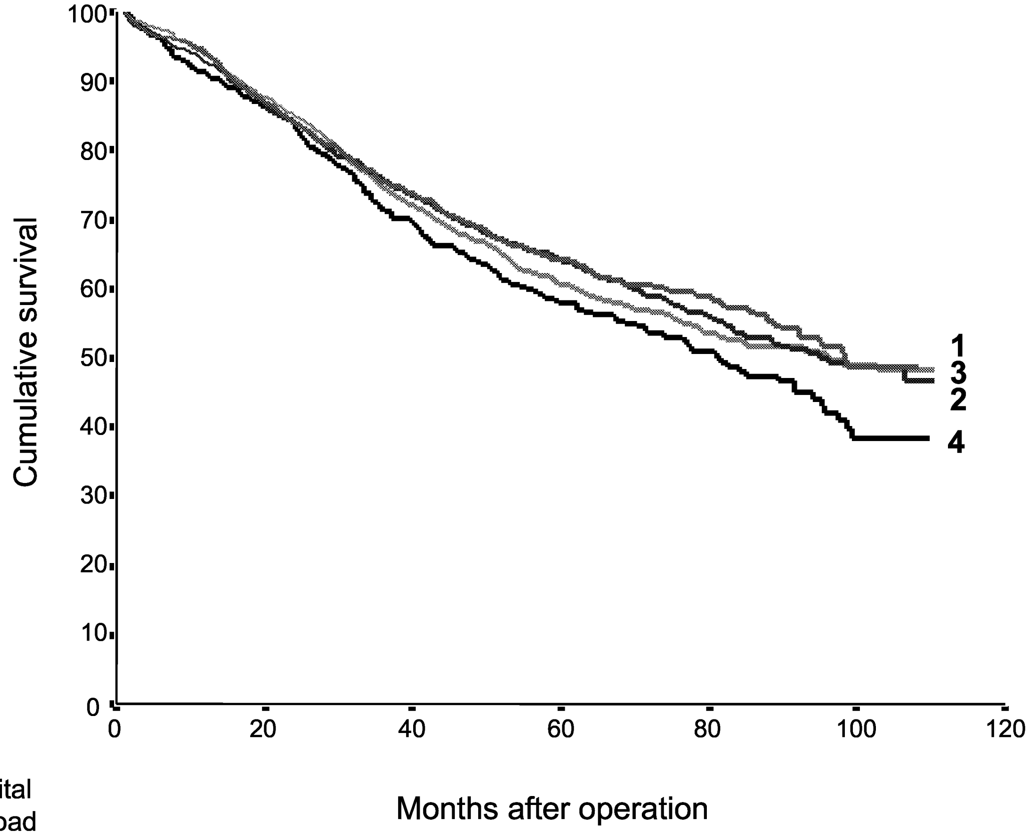
Figure 7 The risk of local recurrence of hospital groups I-IV. The groups are quartiles of the national cohort according to the 3-year LR rate of each hospital. Kaplan-Meier analysis. (One hospital (n = 2) not included because the patients had too short follow-up).

Figure 8 Overall survival of hospital groups I-IV. The groups are quartiles of the national cohort according to the 3-year LR rate of each hospital. Kaplan-Meier analysis. (One hospital (n = 2) not included because the patients had too short follow-up).

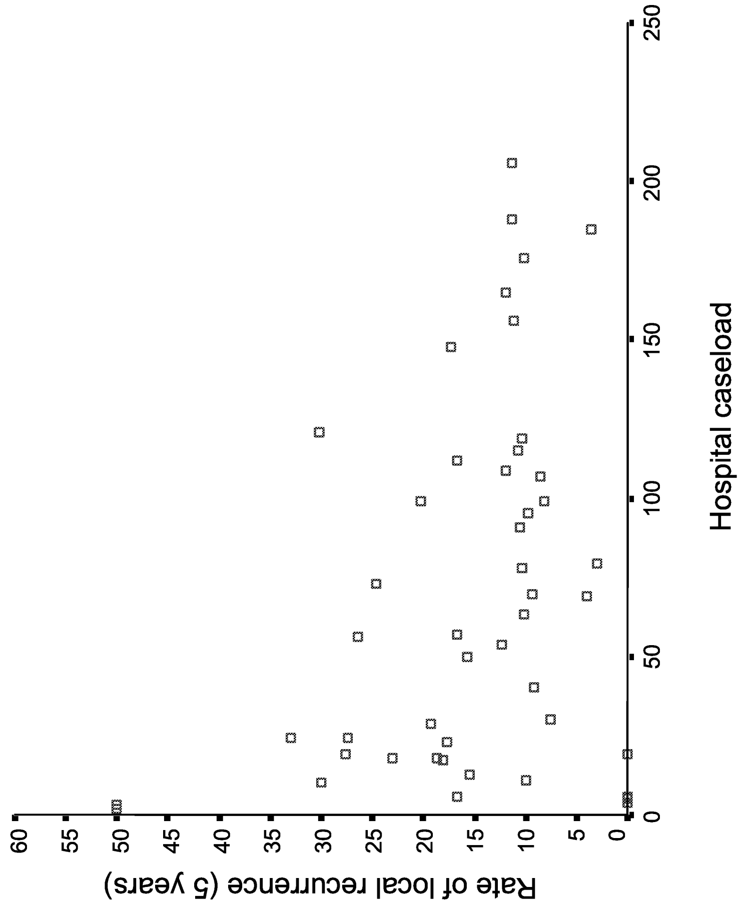


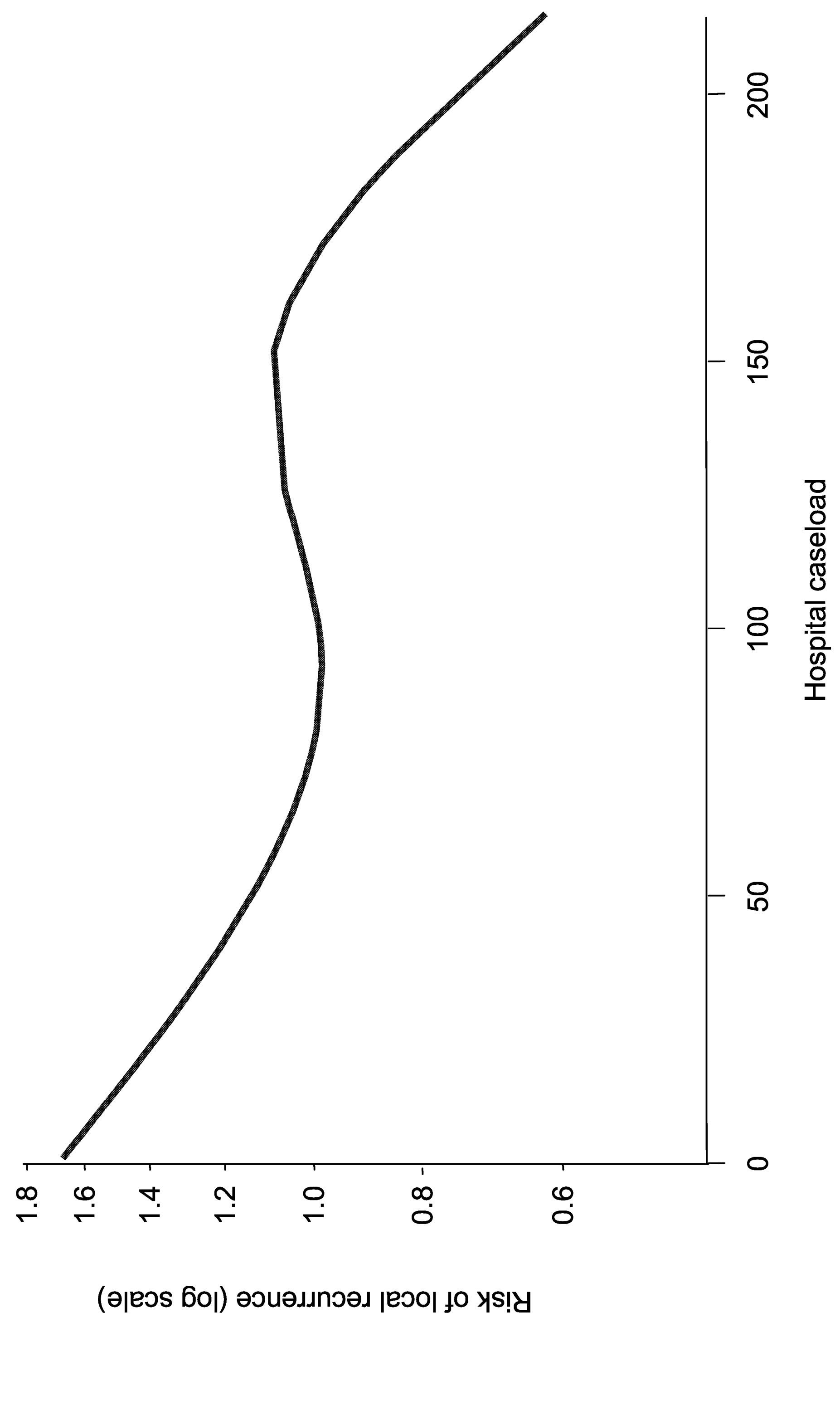

Numbers at risk

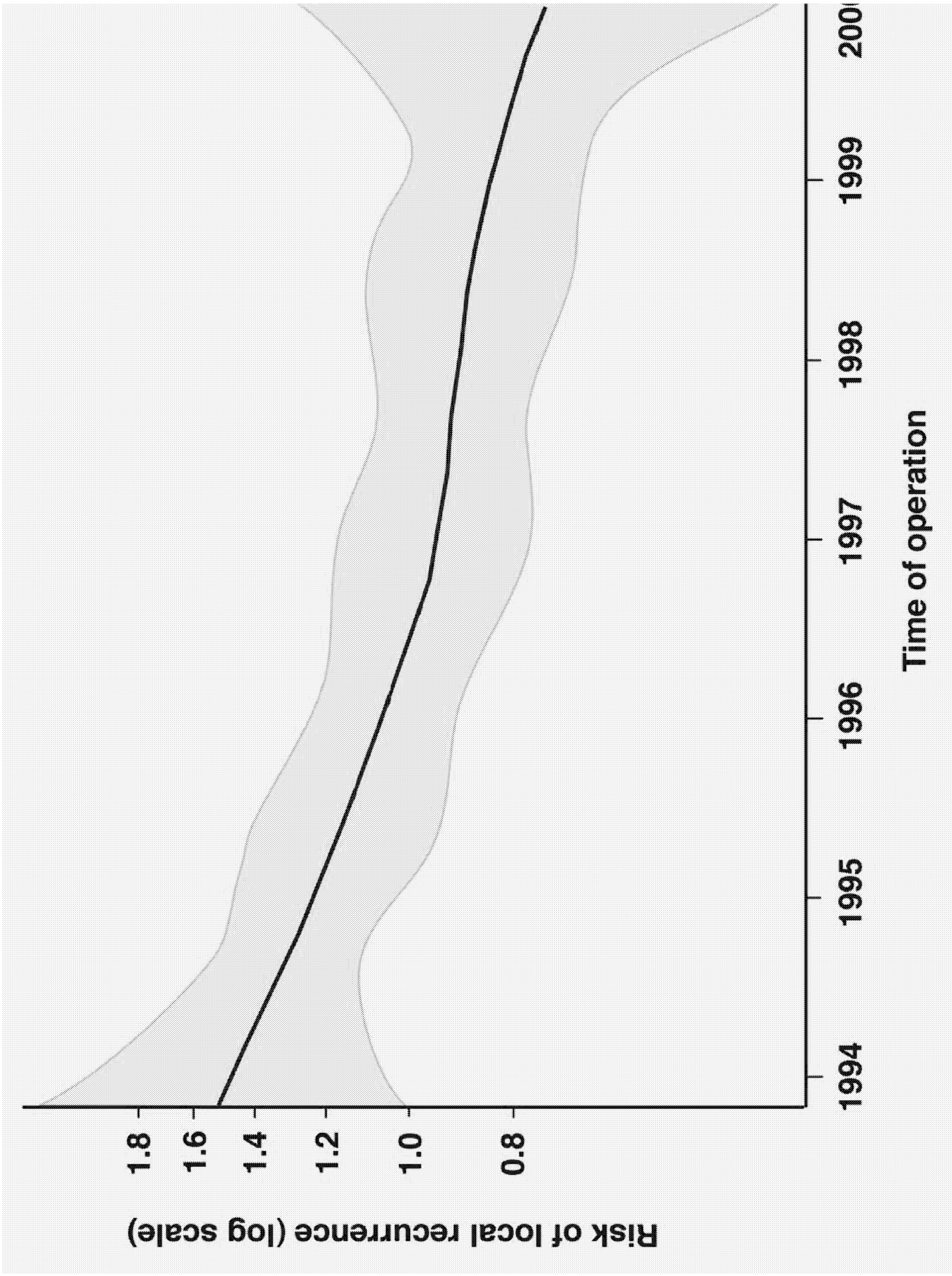
| Hospital caseload group | | | | | |
|---|---|---|---|---|---|
| 1 | 774 | 633 | 411 | 217 | 94 |
| 2 | 854 | 675 | 449 | 269 | 109 |
| 3 | 1352 | 1100 | 678 | 342 | 133 |
| 4 | 408 | 312 | 204 | 115 | 55 |

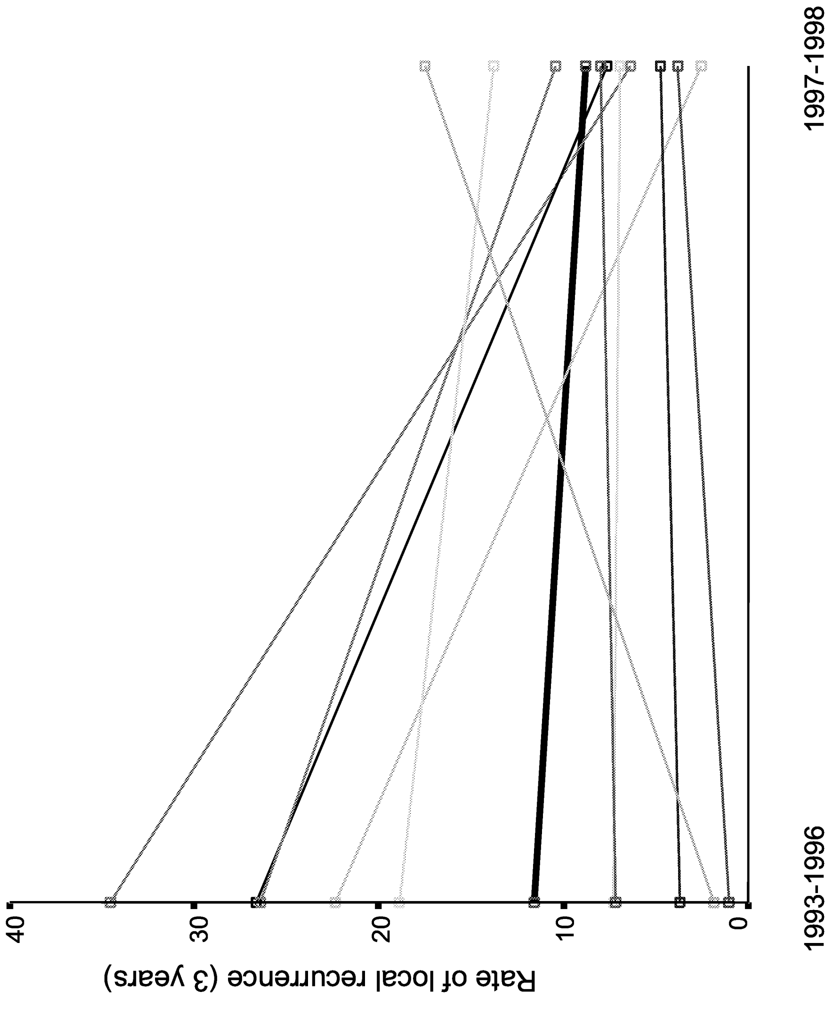


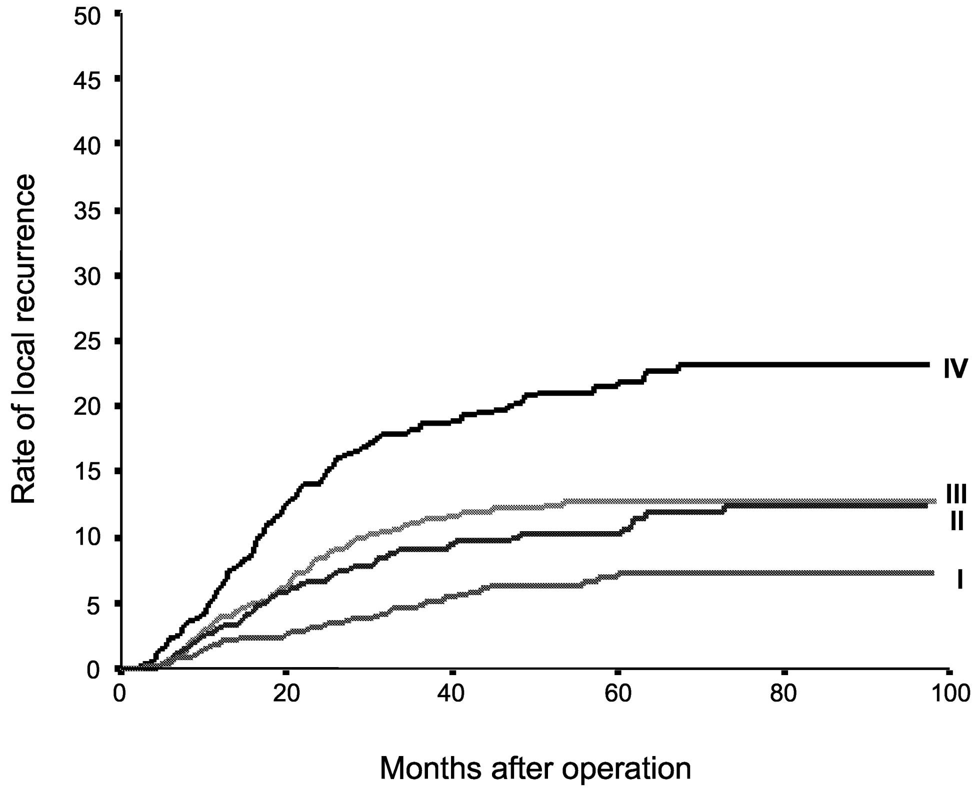

| Hospital caseload group | Numbers at risk | | | | |
|---|---|---|---|---|---|
| 1 | 755 | 656 | 525 | 320 | 169 |
| 2 | 824 | 714 | 571 | 364 | 188 |
| 3 | 1311 | 1149 | 889 | 500 | 241 |
| 4 | 392 | 339 | 258 | 160 | 92 |


Rate of local recurrence (5 years)
Hospital caseload
0
5
10
15
20
25
30
35
40
45
50
55
60
0
50
100
150
200
250

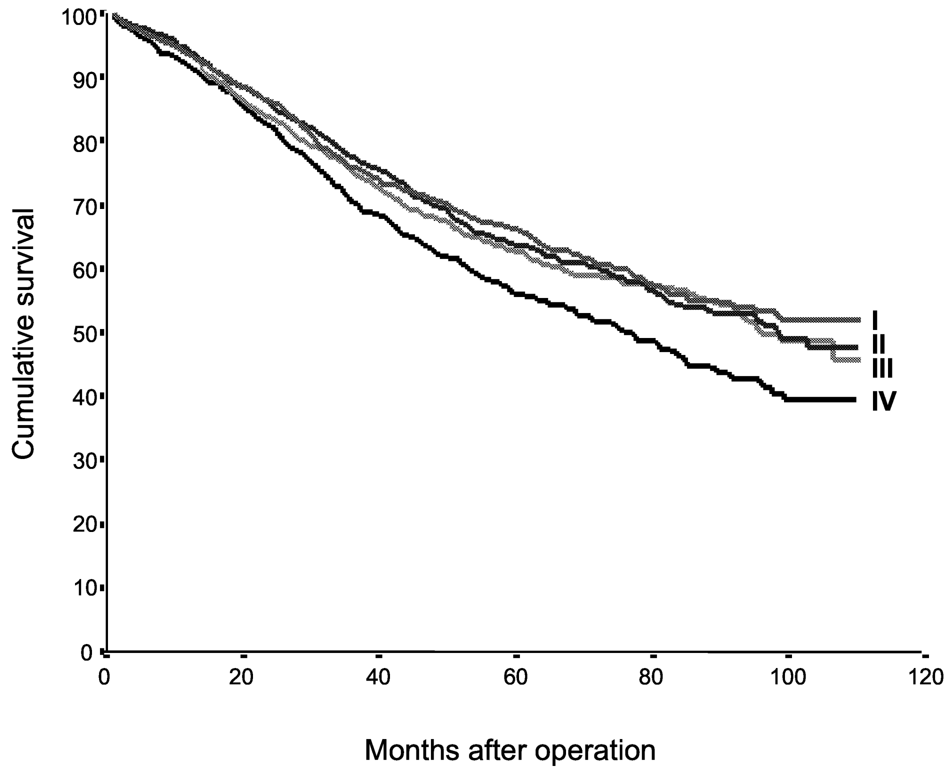

Risk of local recurrence (log scale)
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0
50
100
150
200
Hospital caseload


Risk of local recurrence (log scale)
1.8
1.6
1.4
1.2
1.0
0.8
1994
1995
1996
1997
1998
1999
Time of operation


Rate of local recurrence (3 years)
0
10
20
30
40
1993-1996
1997-1998




| Hospital quartile group | Numbers at risk | | | | |
|---|---|---|---|---|---|
| I | 858 | 722 | 457 | 256 | 99 |
| II | 817 | 675 | 447 | 228 | 101 |
| III | 878 | 711 | 451 | 261 | 113 |
| IV | 833 | 613 | 387 | 198 | 78 |




| Hospital quartile group | Numbers at risk | | | | |
|---|---|---|---|---|---|
| I | 833 | 737 | 580 | 357 | 178 |
| II | 795 | 703 | 567 | 328 | 166 |
| III | 853 | 736 | 585 | 364 | 197 |
| IV | 799 | 682 | 511 | 295 | 149 |

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