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Strategies in Rectal Cancer Treatment

Focus on early rectal cancer and
the influence of age on prognosis

Doctoral thesis
for the degree of philosophiae doctor

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LIST OF PAPERS

- I) Endreseth BH, Wibe A, Svinsås M, Mårvik R, Myrvold HE. Postoperative Morbidity and Recurrence after Local Excision of Rectal Adenomas and Rectal Cancer by Transanal Endoscopic Microsurgery. *Colorectal Disease* 2005; 7: 133-37.
- II) Endreseth BH, Myrvold HE, Romundstad P, Hestvik UE, Bjerkeset T, Wibe A, on behalf of The Norwegian Rectal Cancer Group. Transanal Excision versus Major Surgery for T1 Rectal Cancer. *Dis Colon Rectum* 2005; 48: 1380-8.
- III) Endreseth BH, Romundstad P, Myrvold HE, Hestvik UE, Bjerkeset T, Wibe A, on behalf of The Norwegian Rectal Cancer Group. Rectal Cancer in the Young Patient. *Dis Colon Rectum* 2005 (in press).
- IV) Endreseth BH, Romundstad P, Myrvold HE, Bjerkeset T, Wibe A, on behalf of The Norwegian Rectal Cancer Group. Rectal Cancer Treatment of the Elderly. *Colorectal Disease* 2005 (in press).

These papers will be referred to by their Roman numerals.

ABBREVIATIONS

APR	Abdominoperineal resection
AR	Anterior resection
CRM	Circumferential resection margin
CRC	Colorectal cancer
ERUS	Endorectal Ultrasonography
FAP	Familial adenomatous polyposis
HNPCC	Hereditary non-polyposis colorectal cancer syndrome
IBD	Inflammatory bowel disease
LR	Local recurrence
TEM	Transanal endoscopic microsurgery
TME	Total mesorectal excision
UICC	Union Internationale Contre le Cancer

DEFINITIONS

pTNM classification system (rectal cancer) [1]

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

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

- TX Primary tumour cannot be assessed
- T0 No evidence of primary tumour
- Tis Carcinoma in situ: intraepithelial or invasion of lamina propria
- T1 Tumour invades submucosa
- T2 Tumour invades muscularis propria
- T3 Tumour invades through muscularis propria into subserosa or perirectal fatty tissue
- T4 Tumour directly invades other organs or structures and/or perforates visceral peritoneum

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in 1 to 3 regional lymph nodes
- N2 Metastasis in 4 or more regional lymph nodes

- MX Distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis

Tumour stages (UICC) [1]

- Stage 0 Tis, N0, M0
- Stage I T1-2, N0, M0
- Stage II T3-4, N0, M0
- Stage III Any T, N1-2, M0
- Stage IV Any T, Any N, M1

Dukes' stages [1]

- A
- B
- C
- D

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 or any malignant lymph node to the resection margin.

Involved circumferential margin

CRM \leq 1 mm [2].

Rectal adenoma

A rectal tumour involving the mucosa, not invading the submucosa, thus including Tis.

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 [3]. In the present work only adenocarcinomas are included. In paper I all tumours within 18 cm were included. In paper II all tumours within 15 cm, and in paper III and IV all tumours within 16 cm were included.

Mesorectum

The fatty tissue surrounding the rectum, containing rectal vessels and lymphatic tissue, enveloped by the mesorectal fascia [4].

Total mesorectal excision (TME)

TME is defined as a rectal cancer operation with sharp dissection under direct vision, preserving the mesorectum within an intact endovisceral (mesorectal) fascia. The TME procedure includes resection of the mesorectum together with the rectal tube and in case of anterior resection and Hartmann's procedure dividing these structures distal to the tumour [5].

Transanal endoscopic microsurgery (TEM)

A transanal technique for local excision of rectal tumours, using an operative rectoscope with optic magnification and endoscopic surgical instruments.

Anterior resection (AR)

A rectal resection and a colorectal or a coloanal anastomosis.

Abdominoperineal resection (APR)

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

Hartmann's procedure

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

Curative intent

A procedure with curative intent includes a local excision or rectal resection 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 local rectal cancer excision or a major rectal cancer resection with the aim of cure, including patients with R0 and R1 stage.

Univariate analysis

Simple data descriptions including 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.

Local recurrence (LR)

LR is defined as recurrent disease in the pelvis, including recurrence at the site of the bowel anastomosis or in the perineal wound [6]. LR rates are given as the sum of LR occurring in isolation and concomitant with distant metastases.

Relative survival

Relative survival is defined as the ratio of the observed survival in the study group to the survival of the general population from which they arise, matched for sex, age and period.

Disease-free survival

Disease-free survival is the rate of survivors without verified LR or distant metastasis.

American Society of Anaesthesiologists (ASA) classification [7,8]

ASA class I	the patient is healthy with no systemic disease, and the pathologic process for which operation is to be performed is localized
ASA class II	there is a mild to moderate systemic disturbance caused either by the condition to be treated surgically or by pathophysiologic processes
ASA class III	the patient either has multiple-system disease or well-controlled major systemic disease
ASA class IV	the patient has a severe systemic disorder that is already life threatening and may not be correctable by operation

INTRODUCTION

Rectal cancer treatment in the 1970's and 1980's was characterized by high rates of local recurrence (LR) and poor overall survival [9-11]. The introduction of total mesorectal excision (TME) reduced the rate of LR and improved the survival rates [4, 12, 13]. The results achieved in single centre series with rectal resection and TME technique were superior to those after conventional surgery, even when conventional surgery was combined with preoperative radiation or postoperative (chemo) radiation [10, 14-16].

In 1993 a National Rectal Cancer Registry was established in Norway and in 1994 the Norwegian Rectal Cancer Group was founded. Through educational programmes for surgeons and pathologists TME was implemented as the standard rectal resection technique on a national level. Surveillance of and feedback to the hospitals have improved the results regarding LR and overall survival [17, 18]. There has been a continuous evaluation of the results, and national treatment guidelines based on preoperative tumour staging, intraoperative tumour perforation and postoperative evaluation of the circumferential resection margin (CRM) have evolved [19-21]. Increasing hospital caseloads have proved to influence the rates of LR and overall survival, and as a consequence, the number of treating hospitals has been reduced [22]. In addition, there has been an enhanced focus on the diagnostic radiological modality techniques. Through preoperative staging with evaluation of surgical and pathological prognostic factors, differentiated rectal cancer treatment has developed [23-26].

Preoperative radiation combined with TME technique has proved to reduce the risk of LR, but no benefit in survival has so far been observed in cases of resectable rectal cancer [27, 28]. At present the national guidelines recommend a selective use of (neo)-adjuvant therapy. Rectal

resection with TME technique, without neo-adjuvant therapy, is standard treatment in primary resectable tumours. During the study period, major surgery combined with neo-adjuvant chemoradiation was used for patients with T4 tumours. Adjuvant chemoradiation was used for patients with histopathological verified CRM less than 1 mm or after intraoperative perforation of the tumour [29]. Apart from this, neither radiotherapy nor chemotherapy has been an integrated part of rectal cancer treatment in Norway.

Although the results regarding LR and survival have improved after the introduction of TME, the rates of mortality, morbidity, and the functional disturbances after major surgery are substantial [30-32]. As a consequence, the interest in locoregional treatment of preoperative verified early rectal cancer has increased. Transanal endoscopic microsurgery (TEM) has been introduced into clinical practice and the results achieved are comparable to those after major surgery [33, 34]. Conventional transanal excision has also been recommended as definitive treatment, although there are considerable variation in the rates of LR and overall survival in different series [35, 36].

The prognosis of younger rectal cancer patients is uncertain. A more advanced tumour stage at the time of diagnosis, more aggressive histopathologic characteristics, and inferior rate of survival has been described [37-39]. The results of major surgery in old rectal cancer patients have been evaluated [40-42]. Although higher rates of postoperative mortality and a reduced overall survival compared to younger patients, properly selected elderly patients benefit from major surgery. After the introduction of TME, no national population based series focusing on the influence of age on rectal cancer patients has been published.

In Norway the majority of patients with early rectal cancer have been treated with major rectal resection, and the national treatment guidelines have not differentiated on the age of the patient.

The work presented here is a part of a continuous process, initiated by the Norwegian Rectal Cancer Group, to improve the quality of rectal cancer treatment on a national level through differentiation of management strategies.

AIMS OF THE STUDY

The specific aims of the present study were as follows:

- I. To evaluate the outcome of Transanal Endoscopic Microsurgery (TEM) when introduced as a new treatment strategy for rectal adenomas and for rectal cancer.
- II. To examine the long-term results of transanal excision compared with major surgery in the treatment of T1 rectal cancer.
- III. To characterize clinicopathological issues according to different age groups, to evaluate the results of treatment and to assess whether a change in national treatment guidelines is indicated for young rectal cancer patients.
- IV. To evaluate rectal cancer treatment in the elderly patients and to assess the short and long-term results of major surgery after the implementation of the TME technique on a national level.

METHODOLOGICAL CONSIDERATIONS

Study design

The papers presented in this thesis are based on observational series of patients. Non-randomized clinical studies will always be at risk for potential confounding related to selection of subgroups of patients to different treatment modalities. In order to follow national treatment guidelines [29], randomized design studies were considered not appropriate to evaluate treatment strategies for early rectal cancer, and neither concerning the influence of age on prognosis for rectal cancer.

Papers II-IV are based on a nation-wide registration of relevant clinical information of all incident cases of rectal cancer in the period between 1993 and 2001. Data quality is believed to be high, both in terms of reliability and completeness of ascertainment, and the population-based design in these studies reduces the risk of the potential biases inherent in single institution-based studies. Multivariate analyses have been performed to adjust for potential confounding. Nevertheless, unmeasured confounders could still influence the results.

Paper I – a retrospective single centre series

Paper I in this thesis is based on a cohort of seventy-nine patients treated by TEM for rectal adenoma or rectal cancer at the Department of Surgery, St. Olavs Hospital, University of Trondheim, between January 1994 and November 2001. St. Olavs Hospital is the largest hospital in the county of Sør-Trøndelag and a referral hospital for the counties of Nord-Trøndelag and Møre & Romsdal (Health Region Mid-Norway), including approximately 650000 inhabitants. St. Olavs Hospital was the first hospital in Norway to introduce the TEM technique, and still is the only hospital in Health Region Mid-Norway performing this. The indication for TEM in this series was restricted to sessile rectal adenomas, and patients with

preoperative verified malignant tumours underwent TEM only as they were considered not fit for major surgery because of coexisting disease. The small number of patients reflects the selection of patients considered suitable for this procedure. Although being a referral hospital, the number of patients referred for TEM from other hospitals has been minute. Traditionally distal sessile rectal adenomas have been treated with conventional transanal excision, and sessile adenomas in the middle or upper part of the rectum and early rectal cancer by rectal resection. Due to these alternative treatment options, and possibly insufficient information about this new technique, only a few patients were referred from other hospitals.

Although this is a non-randomized retrospective single-centre series, all the patients treated by TEM after its introduction until end of the study period were included. This consecutive series describes the feasibility and the results achieved when TEM was introduced as a new technique in our department.

Papers II – IV – prospective national population based series

Based on an initiative of the Norwegian colorectal community the Norwegian Rectal Cancer Group was initiated in 1994. In collaboration with The Cancer Registry of Norway a National Rectal Cancer Registry was established. The Norwegian Rectal Cancer Group, consisting of dedicated surgeons, oncologists, pathologists and epidemiologists, is running the Norwegian Rectal Cancer Project. Papers II – IV in this thesis are all parts of this project.

The National Rectal Cancer Registry is population based, and since November 1993 all new cases of rectal cancer have been prospectively registered in a national database. The completeness of this registry is assured through a national obligatory reporting system for malignant diseases to The Cancer Registry of Norway, both for clinicians and pathologists.

Information on patient and treatment characteristics is achieved from the clinicians through their reports to The Cancer Registry of Norway and from a project specific form reported by the surgical departments. Information on tumour characteristics, TNM and R-stage is retrieved from the histopathology reports achieved from the pathologists.

The national follow-up regimen is according to the guidelines of The Norwegian Gastrointestinal Cancer Group [29]. Follow-up time is calculated as patient-months at risk. Date of operation is used as start of follow-up, and endpoints are LR, distant metastases or death regardless of cause.

Follow-up information regarding the use of adjuvant therapy, LR and distant metastasis is retrieved from the project specific forms, the pathology departments' obligatory reports to the Norwegian Cancer Registry and from regular reminders to the surgeons at the treating hospital. The rate of LR is given as the sum of patients with isolated LR and of patients with both LR and distant metastasis. The rate of metastasis includes distant metastasis with or without LR. Local recurrences and distant metastases develop over time, and cumulative rates are given.

Survival rates denote overall (crude), disease-free and relative survival. The Norwegian Cause of Death Registry provides information on time of death. Because of the low rate of autopsies in this national material, leading to possible bias, disease-specific survival is not reported.

All the information retrieved from these various sources regarding patients with rectal cancer is crosschecked by trained staff members and stored in the database at The National Rectal Cancer Registry. The quality of the data is further secured through a continuous evaluation and publication of the results. As a feedback the surgical departments regularly receive their own results together with the national averages for comparison. In order to assure cooperation

between The National Rectal Cancer Registry and the treating hospitals, each surgical department is free to use their own results for scientific purpose. National results are presented at postgraduate courses, focusing on the latest knowledge that can be drawn from the database. Thus, important results of the project are transferred to the surgical community, thus establishing the bases for sharing new treatment strategies.

Statistics

The results regarding categorical variables in Paper I were presented as absolute numbers and frequencies while the sample median and the range were used to describe continuous variables.

In Paper II-IV patient, tumour and treatment characteristics of the different groups were described by frequency tables and compared using Oneway Anova, Mann-Whitney, Pearson Chi-Square or Fisher Exact tests depending on the type of variable and the number of events compared. Missing data were included as “not given”.

LR, metastasis, overall and disease-free survival were estimated by univariate Kaplan-Meier analyses and compared by log rank tests.

In Paper IV, when comparing survival among different age groups of patients with apparent differences in life expectancy due to chronological age, estimates of relative survival were made using the Estève method [43].

Potential prognostic factors were evaluated by multivariate analyses with Cox proportional hazards regression models for LR, metastasis and overall survival. Sensitivity analyses were performed to evaluate missing data by both including and excluding missing data as a separate category. In the final model, statistic significant and/or clinical relevant variables were included.

SUMMARY OF PAPERS

Paper I evaluated the outcome following TEM in a consecutive cohort of the initial seventy-nine patients treated at St.Olavs Hospital between January 1994 and November 2001.

The indications for TEM were rectal adenoma in 72 patients and rectal cancer in seven patients. The median age was 74 years and 32 (41%) patients were classified as ASA 3 and 4. The mean follow up was 24 months (1-95).

Seven patients had complications. Two (2,5 %) patients had peroperative perforation in the intra-abdominal part of the rectum treated by laparotomy. Five (6%) patients had postoperative cardiopulmonal or surgical complications.

Six (8%) patients had gas or faecal incontinence more than one year after the procedure.

Eight (11%) patients with benign pre-operative histopathological examination had cancer, although at an early stage.

The overall LR rate was similar for adenomas and for carcinomas (13%). In the group of patients with free histological margin after TEM for adenoma there were two (3%) recurrences, while none of the patients with free margin after TEM for carcinoma had LR.

In conclusion, TEM is a safe technique well tolerated also by high-risk patients. It should be the preferred method in patients with benign tumours in the middle and upper part of the rectum and in selected cases of early rectal cancer. Benign preoperative histology does not preclude malignancy, and some patients may need further treatment for unexpected malignancy. To avoid remnant tumour tissue after TEM, frozen sections of the margins should be examined during the procedure.

Paper II examined the long-term results of transanal excision compared to major surgery for T1 rectal cancer. This national cohort included all 291 patients with a T1M0 tumour within 15 cm from the anal verge treated by anterior resection (AR), abdominoperineal resection (APR), Hartmann's procedure or transanal excision in the period November 1993 – December 1999. 256 patients were treated by major surgery and 35 patients by transanal excision. None of the patients had neoadjuvant therapy.

11 % of the patients treated with major surgery had glandular involvement. There were no significant differences according to tumour localization, size and differentiation between Stage I and Stage III tumours.

Macroscopic tumour remnants (R2) occurred in 17% (6/35) of the transanal excisions, while major surgery obtained 100% R0 resections. After curative resection the five-year rate of LR was 12% in the transanal excision group compared to 6% after major surgery ($p = 0.010$).

Patients treated with transanal excision were older than patients having major surgery (mean age 77 vs. 68 years ($p < 0.001$), and the overall five-year survival was 70% in the transanal excision group compared to 80% in the major surgery group ($p = 0.04$).

In this study the main problem of transanal excision for early rectal cancer, was the inability to remove all the malignancy. Patients treated with transanal excision had significant higher rates of LR compared to patients undergoing major surgery.

Paper III evaluated the results of treatment for young rectal cancer patients. This national cohort included all 2283 patients younger than 70 years with an adenocarcinoma within 16 cm from the anal verge treated between November 1993 and December 1999. Patients under 40 years (n = 45), 40-44 years (n = 87), 45-49 years (n = 153) and 50-69 years (n = 1998) were compared.

Patients under 40 years had significant higher frequencies of poorly differentiated tumours (27% vs. 12-16%, p = 0.014), N2-stage (37% vs. 13-18 %, p = 0.001) and distant metastases at the time of diagnosis (38 % vs. 19-24%, p = 0.019) compared to older patients.

Among patients treated for cure by AR or APR with TME technique, 56% of the patients under 40 years developed distant metastases compared to 20-26% of the older patients (p = 0.003). Overall five-year survival was 54% for patients under 40 years compared to 71-88% for the older patients (p = 0.029). Age less than 40 years was a significant independent prognostic factor and increased the risk for metastasis and death.

In conclusion, patients under 40 years had a more advanced stage at the time of diagnosis and poor prognosis compared to older patients. Patients younger than 40 years treated for cure more often developed distant metastases and had inferior survival.

Paper IV focused on rectal cancer treatment among patients over 85 years. 4875 patients older than 65 years, treated between November 1993 and December 2001 for a tumour within 16 cm from the anal verge, were included in this national cohort. Patients aged 65-74 (n = 2086), 75-79 (n = 1223), 80-84 (n = 949) and over 85 years (n = 617) were compared.

There were more palliative surgery, local procedures and less surgery for cure (47% vs. 77%, $p < 0.001$) for patients over 85 years compared to younger patients. Five-year relative survival was 36% for patients over 85 years compared to 49% for patients 80-84 years and 60% for patients 65-74 years.

Among patients treated for cure with major surgery and TME technique, the rate of anterior resection decreased by age (67% vs. 46%, $p < 0.001$). Postoperative mortality increased from 3% to 8% ($p < 0.001$). There were no significant differences in the rates of five-year LR, distant metastasis or relative survival.

In conclusion, major rectal cancer surgery can be performed in properly selected patients over 85 years. Although a slight increase in postoperative mortality, these patients had similar rates of LR, distant metastasis and relative survival as younger patients. Rigid treatment guidelines based on high chronological age should be avoided.

GENERAL DISCUSSION

An early rectal carcinoma is defined as TNM stage T1NxMx [44]. T1 tumours less than 3 cm with histological low-risk tumour characteristics are considered suitable for full-thickness local excision by TEM or conventional transanal excision without (neo) adjuvant therapy [34, 44, 45].

The selection of patients with rectal tumours suitable for locoregional treatment is based on preoperative examinations including endoscopy with biopsies and radiological staging.

Paper I demonstrates the challenges of this selection as 11 % of the patients with preoperative presumed adenomas had invasive cancer, although at an early stage. Larger adenomas may have small malignant foci and multiple preoperative biopsies are required. A transmural rather than a mucosal local excision is advisable when possible.

Endorectal Ultrasonography (ERUS) and MRI has proved to be the most accurate modalities in preoperative radiological staging of rectal cancer [23]. The accuracy in determining wall penetration (T-stage) has been reported equivalent, whereas MRI is superior in determining nodal involvement (N-stage). Thus MRI is considered the single most accurate investigation to predict pathological stage in rectal cancer [24].

In early rectal cancer ERUS has been the most commonly used staging modality. However, some recent studies state a lower accuracy in assessing T-stage than previously reported, particularly for early cancers [25, 46, 47]. The assessment of intramucosal and intramural tumours has also been described as difficult when using MRI [26].

On a national basis radiological staging prior to locoregional treatment of early rectal cancer depends on the accessibility of radiological modalities and experience and skills of the surgeons. A wide variation in the accuracy of preoperative staging is likely.

While major surgery for T1 rectal cancer, as presented in Paper II, assures complete removal of the tumour, the ability of locoregional treatment to achieve R0 status was significantly impaired. All eight T1 tumours treated by TEM in paper I were completely excised, and 80 percent (51/64) of the adenomas had a free margin in the line of resection. After transanal excision of T1 tumours in paper II, there was only 46 percent R0 stage after the procedure. The curative intent in the treatment of fit patients with T1 rectal cancer is absolute, and a complete removal of the tumour is imperative. Transmural excision with an adequate margin of clearance and intraoperative frozen section of the tumour margins are mandatory in order to verify radical excision.

The major concern regarding locoregional treatment of early rectal cancer has been the possibility of leaving metastatic lymph nodes after the procedure. The overall risk for Stage III disease in patients with T1 rectal tumours is about 10 % [44, 48], similar to the findings in Paper II.

Several previous series have evaluated potential predictors in order to differentiate between Stage I and Stage III rectal cancer. Well-established high-risk tumour characteristics are poor differentiation of the tumour, lymphovascular infiltration and mucinous subtype [44, 48, 49]. More recently the Sm-classification has been developed, and sessile T1 tumours with invasion to the lower one-third of the submucosa are considered as high-risk tumours [44, 50].

The information regarding these risk factors is mainly obtained from the postoperative histopathological examination of the resected T1 lesion. In Paper II neither tumour differentiation nor other preoperative verified variables, such as tumour diameter and distance from anal verge, were significant predictors in the differentiation between Stage I and Stage III rectal cancer.

The standard histopathological description of a locally excised T1 lesion should include adequate information regarding these high-risk tumour characteristics, and a close collaboration between the pathologist and the surgeon is important.

Fit patients with inadequate resection margin or high-risk tumour characteristics after locoregional treatment of early rectal cancer should receive additional treatment in order to obtain satisfactory treatment results. The long-term results after major surgery for failed locoregional treatment are inconsistent, although immediate rather than salvage surgery at the time of verified LR ought to be preferred [35, 51-53]. Adjuvant (chemo) radiation has also been advocated in single series on T1 tumours with adverse factors [45, 54, 55].

The rates of LR and survival after transanal excision of T1 rectal cancer presented in Paper II are inferior to those after major surgery. As for other series on locoregional treatment of early rectal cancer, these findings are based on analyses of non-randomized cohorts of patients. Although some series evaluating locoregional treatment of T1 rectal cancer present results comparable to those after major surgery, there is a significant variation in the rates of LR and survival. The results achieved depend upon the selection criteria, surgical approach, use of adjuvant therapy, and study design.

The complication rates and the functional results after locoregional treatment are superior to those after major surgery [34-36, 56]. In the presented series 41% of the patients selected for TEM were high-risk patients classified as ASA 3 or 4, and the patients treated by transanal excision in Paper II were significantly older than those undergoing major surgery.

The selection of patients has been based on preoperative clinical evaluation. Although increased comorbidity among the locoregional treated patients must be assumed, the rates of complications and postoperative mortality were low.

Accurate preoperative staging, radical excision through adequate surgical technique and exact histopathological evaluation of the resected specimen are of paramount importance in order to achieve acceptable results after locoregional treatment of early rectal cancer. Locoregional treatment without adjuvant therapy may be a safe alternative to major surgery in cases with completely excised T1 low-risk tumours.

Paper III confirmed the finding of previous series considering young rectal cancer patients as a high-risk group with inferior prognosis [39, 57, 58]. However, previous studies frequently include both colon and rectal cancer patients, and none of the former studies have reflected the outcome after standardized rectal cancer surgery with TME technique.

The upper age limit of young patients in this perspective has been vague, but most series have classified patients under 40 years as young. In order to define a potential high-risk group among younger rectal cancer patients, this national cohort focused on the entire range of under average aged patients.

Rectal cancer patients under 40 years have higher frequencies of advanced disease at the time of diagnosis. Information on time from symptoms to diagnosis was not stated in this cohort, and diagnostic delay may have influenced on the shift towards more advanced disease among younger patients [38, 59]. The similarity in distribution of tumour size and T-stage between the different age groups in the present series opposes this as the solitary explanation of this finding.

The distribution of patients with regional lymph node metastases (Dukes' C) was similar, but the rate of patients with N2 stage, poorly differentiated tumours and distant metastases, were significantly higher among the youngest patients. Advanced tumour stage is correlated with inferior prognosis, and the overall five-year survival among all patients less than 40 years was only 38 percent, significantly inferior compared to the older.

Predisposing factors such as IBD, FAP, HNPCC or a family history of colorectal cancer (CRC) have been described as a frequent finding among young CRC patients [38]. High-risk patients with IBD or FAP should preferably be treated with proctocolectomy before they

develop invasive carcinoma, and in this cohort only three patients had IBD or FAP at the time of diagnosis.

Information on HNPCC or family histories of CRC was not available. Carcinomas in HNPCC patients tend to be multiple and located in the proximal colon [58, 60]. In this series of rectal cancer patients the rate of synchronous cancer was similar in the different age groups. This contradicts that HNPCC or multifocal cancer, as seen in familiar cancer syndromes, was more frequent among the youngest patients.

Due to the high rate of distant metastases at the time of diagnosis only 40 percent of the youngest patients in this series underwent a rectal resection with curative intent. Although there were no differences in the distribution of tumour stage or R-stage between the groups of patients treated for cure, the prognosis was still inferior among patients under 40 years. More than half of the youngest patients developed distant metastasis, and the five-year overall survival was significant inferior.

Biologically more aggressive cancer and reduced regulation of tumour growth might account for the advanced stage at the time of diagnosis and the inferior prognosis among young rectal cancer patients [61, 62]. The indication for (neo) adjuvant therapy as a part of the standard treatment in this subgroup of patients has to be evaluated.

During the last decades both the incidence of rectal cancer and the life expectancy have been increasing in Norway. In 1997-2001 the maximum age-specific incidence of rectal cancer in Norway was observed among patients aged 75-79 years in both genders [63], and at the time of diagnosis more than 40 percent of rectal cancer patients were older than 75 years. As a consequence, the number of fragile rectal cancer patients with additional systemic disease has and probably will continue to increase. Although the national results of rectal cancer treatment have improved after standardisation of surgical treatment with TME technique, a more selective and differentiated treatment strategy may be required among older patients with comorbidity. In order to guide clinicians concerning strategy, Paper IV focused on the characteristics and results of treatment among elderly rectal cancer patients.

The rate of surgically treated patients decreased by age. Coexisting medical disorders are known to increase with age and influence on this finding. Diagnostic delay among the elderly, leading to a more advanced tumour stage at the time of diagnosis and inferior rates of resection should also be considered [64, 65]. In this series the staging of patients not undergoing surgery was inaccurate, and among patients undergoing surgery the rate of inaccurate staging increased by age. Age related differences in stage at the time of diagnosis are possible.

Although the distribution of Dukes' stage was similar in the age groups of surgical treated patients, there were significant differences in type of surgical procedure. Locoregional and palliative surgery was more common among the older patients, and the rate of curative resections decreased by age. The age of the patients and the increased comorbidity have influenced on the surgeons selection of operative procedure, and less extensive surgery was done in older patients.

When evaluating the entire cohort of patients older than 65 years, the relative survival decreased by age. This indicates that the strength to recover from rectal cancer and its treatment decreased by age, although inferior effort and quality of treatment among the oldest patients might have influenced on this finding.

Adequate evaluation of the patient, awareness of the alternative treatment options and their expected results, is mandatory also among elderly rectal cancer patients. The selection of treatment should be based on accurate preoperative tumour staging, geriatric and anaesthesiologic considerations and the patients informed choice.

The rate of patients undergoing curative major surgery with TME technique decreased by age, but still this treatment was achieved in one-third of the patients aged over 85 years. Although high age has showed no negative effect on the functional results and rate of anastomotic leakage in recent series [64, 66-68], the rate of restorative resections decreased by age, and more than half of the oldest patients had a colostomy. The oldest patients may have particular difficulties in stoma care, and a restorative resection should be considered when the patient is fit for major surgery.

Despite higher postoperative mortality among patients aged over 80 years, the results regarding LR, metastasis and relative survival were similar among the different age groups of patients treated with curative major surgery. The higher rate of postoperative mortality among the oldest is correlated to the selection of patients, and other series on rectal cancer treatment of the elderly contradict this finding [40-42]. Irrespective of age, properly selected patients benefit from major rectal resection with TME technique.

CONCLUSIONS

The present studies illustrate the pros and cons associated with locoregional treatment of rectal adenomas and early rectal cancer:

- Preoperatively benign histology and adequate radiological staging do not preclude malignancy.
- The prediction of glandular metastasis, before or after local excision, is difficult, however essential, as 11% of the patients with T1M0 tumours have Stage III disease.
- The main problem of transanal excision of early rectal cancer is the inability to achieve R0 status, and after curative excision the rate of local recurrence is significantly higher than after major surgery.
- To avoid remnant tumour tissue after locoregional treatment, frozen sections of the margins should be examined during the procedure.
- TEM is a safe technique, also in high-risk patients, and should be the treatment of choice in patients with benign tumours in the middle and upper part of the rectum, and in selected cases of early rectal cancer.

Furthermore, the studies illustrate the influence of age on the prognosis in rectal cancer patients:

- Patients under 40 years have a more advanced stage at the time of diagnosis and poor prognosis compared to older patients. Patients under 40 years treated for cure with TME technique more often develop distant metastases and have inferior survival.

- Major rectal cancer surgery with TME technique can be performed in properly selected patients over 85 years. Although a slight increase in postoperative mortality, these patients have similar rates of local recurrence, distant metastasis and relative survival as younger patients.

PERSPECTIVES

The enhanced national focus on rectal cancer and the introduction of the TME technique has improved the prognosis for rectal cancer patients. Through a continuous evaluation of the treatment results with focus on distinctive subgroups of patients, further improvement can be obtained.

To further assess locoregional treatment as an optional treatment of early rectal cancer large series of patients are required. The number of Norwegian hospitals performing TEM has increased, and a prospective national study, evaluating the results achieved by TEM, would be of importance concerning future national treatment strategies for early rectal cancer.

In locoregional treatment of T1 rectal cancer the difficulties in predicting potential glandular metastasis is of major concern. The large number of T1 tumours treated by major surgery with TME technique without chemo-radiation in the presented material is unique. Reassessment of the histopathological preparations, with evaluation of established and alternative predictive factors for Stage III disease among patients with T1 tumours, would be of importance.

The significant inferior prognosis among rectal cancer patients under 40 years requires further evaluation. Potential genetic factors related to reduced cell repair or tumour control and the indication for adjuvant therapy must be assessed.

An enhanced focus on treatment of rectal cancer patients high at age and/or with severe comorbidity is justified. Alternative treatment regimens, including neo-adjuvant chemoradiation and locoregional treatment, should be evaluated.

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Paper I

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Paper II

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Paper III

Rectal Cancer in the Young Patient.

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ABSTRACT

Purpose The purpose of this national study was to evaluate the results of treatment for young rectal cancer patients.

Methods This prospective study from the Norwegian Rectal Cancer Project includes all 2283 patients younger than 70 years with adenocarcinoma of the rectum from November 1993 to December 1999. Patients under 40 years (n = 45), 40-44 years (n = 87), 45-49 years (n = 153) and 50-69 years (n = 1998) were compared for patient and tumor characteristics and five-year overall survival. Patients treated for cure (n = 1354) were evaluated for local recurrence, distant metastasis, and disease-free survival.

Results Patients under 40 years had significant higher frequencies of poorly differentiated tumors (27 percent vs. 12-16 percent, $p = 0.014$), N2-stage (37 percent vs. 13-18 percent, $p = 0.001$) and distant metastases (38 percent vs. 19-24 percent, $p = 0.019$) compared to older patients. Among those treated for cure, 56 percent of the patients under 40 years developed distant metastases compared to 20-26 percent of the older patients ($p = 0.003$). Overall five-year survival was 54 percent for patients under 40 years compared to 71-88 percent for the older patients ($p = 0.029$). Age less than 40 years was a significant independent prognostic factor and increased the risk for metastasis and death.

Conclusions Patients under 40 years had a more advanced stage at the time of diagnosis and poor prognosis compared to older patients. Young patients treated for cure more often developed distant metastases and had inferior survival.

(Keywords: Rectal cancer, young patients, distant metastasis, overall survival)

INTRODUCTION

Over the last decades the incidence of colorectal cancer (CRC) has increased, and at present it is the second most frequent cancer in Norway.¹ One-third of the CRC patients have rectal cancer, with a world standardized age-adjusted incidence rate in 1997-2001 of 16 per 100 000 for males and 10 per 100 000 for females. The mean age of rectal cancer patients is 70 years. The age-specific incidence of rectal cancer increases sharply after the age of 50 years, and in Norway 5 percent of the patients are 50 years or younger.

After the introduction of total mesorectal excision (TME) the results of rectal cancer treatment have improved radically.^{2,3} In 1993 a National Rectal Cancer Registry was established in Norway. Treatment guidelines based on tumor stage and surveillance of and feedback to the hospitals have resulted in improved results according to local recurrence and overall survival.⁴ Neoadjuvant radiotherapy is standard treatment for patients with T4 tumors, and adjuvant radiotherapy is used for patients with involvement of the circumferential resection margin (CRM) or after intraoperative perforation of the tumor. Apart from this, neither radiotherapy nor chemotherapy has so far been recommended as an integrated part of rectal cancer treatment in Norway. The national treatment guidelines have not differentiated on the age of the patient.

The prognosis of younger patients with colorectal cancer is uncertain. Although the upper age limit of these patients remains undefined, most studies have classified patients under 40 years as young. Some studies have revealed a more advanced tumor stage at the time of diagnosis,⁵⁻⁸ more aggressive histopathologic characteristics,⁹⁻¹⁶ and inferior rate of survival¹⁷⁻²¹ in younger patients when compared to older ones. Other studies contradict these findings.²²⁻³⁵ Most of these studies are single institution series, and to our knowledge, no national

population based study, focusing on rectal cancer in the young after the introduction of the TME technique, has been published.

The aims of this study were 1) to characterize the clinicopathologic issues according to different age groups among younger rectal cancer patients, 2) to evaluate the results of treatment, and 3) to assess whether a change in treatment guidelines is indicated for young rectal cancer patients.

METHODS

This study was a part of the Norwegian Rectal Cancer Project initiated in 1993. Since then all new cases of rectal cancer have been prospectively registered in a national database according to patient, tumor and treatment characteristics. Detailed descriptions of the project have been published by Wibe *et al.*⁴

Patient characteristics

In the period November 1993 – December 1999 a total of 5297 patients, with a mean age of 70 years, were treated for invasive rectal adenocarcinoma. Patients under 70 years of age were selected, resulting in a study population of 2283 patients (43 percent) (Table 1). For further analysis these patients were divided into four subgroups according to age (< 40, 40-44, 45-49 and 50-69 years). One thousand three hundred and fifty four patients with a rectal adenocarcinoma within 16 cm from the anal verge, treated for cure by anterior resection (AR) or abdominoperineal resection (APR) with total mesorectal excision (TME), were included in the final analyses (Table 2). Rectal cancer surgery was performed at 47 hospitals.

Definitions

Patient and treatment characteristics were collected from the project specific forms.

Information on tumor differentiation, TNM³⁶ and R-stage were retrieved from the histopathology reports. The R0-stage (residual tumor staging) denotes the group of patients with a resection margin >1 mm, the R1-stage includes specimens with a margin 0-1 mm, the RX-stage includes specimens where the circumferential resection margin was not specified and R2-stage patients had macroscopic tumor remnants as denoted by the surgeon.

A resection with a curative intent includes all resections where the surgeon had the aim of cure, thus including patients with microscopic tumor involvement of the resection margin and patients with intraoperative perforation of the tumor.

The tumor level is given as the distance from the lower tumor border to the anal verge. The tumor diameter denotes maximum tumor diameter after fixation of the excised specimen.

The Norwegian Cause of Death Registry provided information on time of death.

Postoperative mortality denotes mortality rates within 30 days of the procedure.

Synchronous cancer denotes concomitant active malignant disease at the time of the operative treatment for rectal cancer.

Local recurrence was defined as clinically or histopathologically verified recurrent disease in the pelvis, including the site of the bowel anastomosis and of the perineal wound, and was retrieved from the project specific forms or the pathology departments obligatory reports to the Norwegian Cancer Registry. The rate of local recurrence is given as the sum of the patients with isolated local recurrence and the patients with both local recurrence and distant metastasis. Metastases denote recurrent disease outside the pelvis. The rate of metastasis includes distant metastasis with or without local recurrence. Survival rates denote overall (crude) and disease-free survival.

The follow-up regimen was according to the guidelines of The Norwegian Gastrointestinal Cancer Group.³⁷ Follow-up time was calculated as patient-months at risk. Date of operation was used as start of follow-up, and endpoints were local recurrence, distant metastases or death regardless of cause. The range of follow-up was 24-97 months. None of the patients were lost to follow-up. End of follow-up was 31 December 2001.

Preoperative radiotherapy denotes a regimen of 2 Gy x 25 and postoperative radiotherapy denotes 2 Gy x 25 and concomitant bolus of 5-fluorouracil.

Statistics

Patient, tumor and treatment characteristics of the different age groups were described by frequency tables and compared using Fisher Exact or Oneway Anova tests (Table 1 and 2). Missing data were included as “not given”.

Local recurrence, metastasis, overall and disease-free survival were estimated by univariate Kaplan-Meier analyses and compared by log rank tests (Table 3 and 4).

Potential prognostic factors were evaluated by multivariate analyses with Cox proportional hazards regression models for local recurrence, metastasis and overall survival (Table 5). Sensitivity analyses were performed to evaluate missing data by both including and excluding missing data as a separate category. In the final model statistic significant and/or clinical relevant variables were included.

Analyses were performed using SPSS[®] version 12.0 (SPSS Inc., Chicago, IL).

RESULTS

All patients

Of the 2283 patients under 70 years diagnosed with rectal cancer, 45 patients were younger than 40 years, 87 patients 40-44 years, 153 patients 45-49 years and 1998 patients 50-69 years (Table 1).

Three patients had predisposing conditions. Two patients had familiar adenomatous polyposis and one had ulcerative colitis, these patients were treated with proctocolectomy. The distribution of synchronous cancer was not significantly different between the age groups (data not given). The male/female ratio was lower in the two youngest age groups.

Patients under 40 years of age had a significant higher frequency of poorly differentiated tumors, N2-stage and Dukes' stage D compared to the older patients.

The overall five-year survival was 38 percent in the group of patients younger than 40 years of age, 70 percent for patients between 40 and 44 years, 62 percent for patients between 45 and 49 years and 56 percent for the group of patients between 50 and 69 years ($p = 0.004$) (Table 3, Fig 1). The median survival for patients younger than 40 years was 40 months.

Patients treated for cure

Among the 1354 patients treated for cure, 18 patients were younger than 40 years, 54 patients 40-44 years, 92 patients 45-49 years and 1190 patients 50-69 years (Table 2).

The male/female ratio was lower in the two youngest age groups. The frequency of poorly differentiated tumors was higher for patients under 40 years, 22 percent vs. 7-19 percent for older patients. Apart from this, there were similar tumor characteristics in the four age groups.

There were no differences in the rate of intraoperative perforation or patients with R1 status; however, postoperative radiotherapy was more often used in the youngest patients.

The five-year rate of local recurrence was 20 percent for patients under 40 years compared to 8-18 percent for older patients (Table 4).

Distant metastases occurred in 56 percent of the patients under 40 years, 22 percent for patients 40-44 years, 20 percent for patients 45-49 years and 26 percent in the group of patients between 50 and 69 years (Table 4, Fig 2).

Overall five-year survival was 54 percent, 88 percent, 76 percent and 71 percent (Table 4, Fig 3), and disease-free survival was 44 percent, 74 percent, 70 percent and 61 percent, in the same four groups respectively.

The risk of local recurrence was increased in males compared to females by a factor of 1.4 (Table 5). Age and tumor differentiation did not influence the rate of local recurrence. Young age had a significant influence on the risk of developing distant metastasis. Being less than 40 years of age increased the risk of distant metastasis by a factor of 5.1 compared to patients between 40 and 44 years. Higher age did not influence the rate of distant metastasis, and neither did tumor differentiation.

Mortality was 50 percent higher in males than in females. The highest mortality was found in the patients less than 40 years of age, being increased by a factor of 6.2 compared to the patients aged 40-44 years. Tumor differentiation influenced overall survival, and patients with poorly differentiated tumors had an increased risk of death by a factor of 1.6 compared to patients with well or medium differentiated tumors.

DISCUSSION

This study on rectal cancer describes patients less than 40 years of age as a high-risk group with inferior prognosis. Several previous studies on colorectal cancer have demonstrated poor prognosis in the young patients,¹⁷⁻²¹ although few studies report the influence of age on clinicopathologic features and prognosis among the entire range of under average aged rectal cancer patients.

The majority of the studies on this topic are retrospective single institution series. Population based studies include both colon and rectum cancer patients treated during longer time periods between 1943 and 1999.^{6,14,24,26,27,31,33,34} The treatment protocols may have changed during and after these periods. None of the former studies reflect the outcome of current surgical practice for rectal cancer treatment using TME. The present study was based on a prospective national cohort following standardized TME for rectal cancer.

Over the last decades, the median age of colorectal cancer patients in Norway has increased.³⁸ The median age in this national cohort from 1993 to 1999 was 72 years. This may in part explain the low frequency of rectal cancer patients less than forty years of age, 0.9 percent in this series. Older colorectal population based series, and series with longer time-span, report a higher frequency, ranging from 1.1 to 5.4 percent.^{6,26,27,31,33,34,35} Compared to colon tumors the proportion of rectal tumors is lower in patients below the age of 40 years.²⁶ Higher frequencies in single institution series may be the result of referral-center experience or because of different age ranges in series from developing countries.^{10-12,16}

In the literature an average of 16 percent of the young colorectal carcinoma patients have predisposing factors (inflammatory bowel disease, familial adenomatous polyposis (FAP) or hereditary non-polyposis colorectal cancer syndrome (HNPCC), and 23 percent have a family

history of colorectal cancer.¹² Some series find a similar rate of family history in young and old colorectal cancer patients.^{7,9,18} Different molecular biological features of the tumor, with higher frequency of acquired⁹ or inherited microsatellite instability as in HNPCC²³ in the young have been described.

In this cohort only three patients had predisposing conditions (FAP or ulcerative colitis) at the time of diagnosis, indicating that these high-risk groups achieve adequate treatment (proctocolectomy) before they develop invasive rectal carcinoma. Information on HNPCC or family histories of colorectal carcinoma was not available. HNPCC carcinomas tend to be multiple and have a proximal location in the colon,^{9,14,21,31} but there were no differences in the distribution of synchronous cancer between the age groups in this series. Multifocal cancer, as seen in familiar cancer syndromes, was not more frequent among the young rectal cancer patients.

Higher frequencies of tumors in advanced stage at the time of diagnosis,^{5-9,12-14,16-18,20,21,30,35} and of poor differentiation,^{6,7,9-22,24,35} have been pointed out in several studies on young colorectal patients. This is consistent with the present series where a significant higher proportion of patients with multiple regional glandular metastases (N2), distant metastases (Dukes` D) and poorly differentiated tumors were found among patients under 40 years. In this study the high proportion of young patients presenting with an advanced stage of disease correlates with a higher incidence of histologic aggressive tumors. Other histopathologic indicators of aggressive tumorbiology include mucinous component, signet-ring cell carcinoma, perineural, vascular and lymphatic invasion.^{11-15,28,29,32} These variables have not been routinely reported in this national study. Neither have the molecular biologic characteristics known to regulate tumor growth.²³

Diagnostic delay has been argued to be another factor causing more advanced disease in young colorectal patients.^{8,11,17,25,27,28} Time from symptoms to diagnosis was not stated in this cohort, but there were no significant differences between the age groups according to T-stage or tumor diameter at the time of diagnosis.

Young patients with colorectal cancer are reported to have a poor survival compared to older patients.^{12,16-18,20,21} The univariate analysis on overall survival in this series, including all patients diagnosed with rectal cancer, shows a significant lower survival rate in patients under 40 years. It is well known that advanced tumor stage is correlated with inferior survival.^{8,11,16-18,20,29,32} Biologically more aggressive cancer rather than diagnostic delay appears to account for the advanced stage at the time of diagnosis leading to poor survival rates in young rectal cancer patients, and this phenomenon may also explain inferior prognosis for young patients treated for cure.

Previous reports from this project have demonstrated the effect of hospital caseload and inadvertent perforation of the tumor on outcome of rectal cancer treatment.^{39,40} The present results showing inferior prognosis for patients less than 40 years were not related to low hospital caseload or high rates of perioperative perforation. These risk factors had similar distribution in the different age groups (data not given).

The use of postoperative radiotherapy was significantly higher in the youngest age group. This may be explained by the fact that the treating hospitals have omitted the current national treatment guidelines in an effort to give the youngest patients what they presumed was the best possible treatment. Due to the small number of younger patients, the effect of adjuvant radiotherapy was indistinct. There were no significant differences between the age groups regarding local recurrence, and despite a more frequent use of postoperative radiotherapy, the youngest patients still had the highest rate of local recurrence.

Some series on colorectal cancer comparing young and old patients demonstrate similar overall survival rates.^{23,25,26,33} These series state no differences in stage and histopathologic characteristics. Other studies state similar survival when comparing young and old patients with similar tumor stage.^{8,9,11,13,15,24,28,35} In the present analyses on patients treated with curative intent there were no significant differences according to T-stage, N-stage or Dukes' stage between the age groups, but a significant higher incidence of poorly differentiated tumors among the younger patients.

Although the number of young patients is small, this national cohort suggests age as a significant and independent prognostic factor according to metastasis and survival for rectal cancer. Patients under 40 years had five times higher risk of metastasis and six times higher risk of death compared to patients between 40 and 44 years. The youngest rectal cancer patients seem to have additional negative prognostic factors, not related to histopathologic findings or tumor stage. Genetic factors, related to reduced cell repair or tumor control, must be considered.^{9,23} This theory supports the present findings of more N2 stage and Dukes' D at diagnosis as well as more distant metastases following curative treatment in patients younger than 40 years.

CONCLUSION

This national cohort study of rectal cancer patients found that patients under 40 years had poor prognosis compared to older patients. The younger patients not only had more advanced stage at the time of diagnosis, but also patients treated for cure more often developed distant metastases and had inferior survival. Young rectal cancer patients may have more aggressive tumor biology and possibly reduced regulation of tumor growth.

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Table 1 Patient and Tumor Characteristics of 2283 Patients under 70 Years of Age with Rectal Cancer

	< 40 years	40 - 44 years	45 - 49 years	50 - 69 years	P*
	n (%)	n (%)	n (%)	n (%)	
Age, mean(range)	34(16-39)	43(40-44)	48(45-49)	62(50-69)	
Gender					< 0.001**
Female	26 (58)	54 (62)	67 (44)	788 (39)	
Male	19 (42)	33 (38)	86 (56)	1210 (61)	
Lower border (cm), mean(range)	9.6(0-18)	8.6(1-18)	9.2(0-19)	9.4(0-20)	0.395 ***
Tumor diameter (cm), mean(range)	5.1(0-10)	4.5(1-10)	4.6(1-11)	4.5(0-20)	0.193 ***
Differentiation					
G1 (well)	4 (9)	4 (5)	11 (7)	147 (7)	0.782 **
G2 (medium)	24 (53)	61 (70)	104 (70)	1430 (72)	0.056 **
G3 (poor)	12 (27)	14 (16)	24 (16)	237 (12)	0.014 **
Not given	5 (11)	8 (9)	14 (7)	184 (9)	
T-stage					
T1	3 (7)	13 (15)	14 (9)	168 (8)	0.212 **
T2	9 (20)	10 (12)	41 (27)	406 (20)	0.041 **
T3	21 (47)	44 (51)	72 (47)	1082 (54)	0.256 **
T4	12 (27)	17 (20)	22 (14)	312 (16)	0.167 **
Not given	0 (0)	3 (3)	4 (3)	30 (2)	
N-stage					
N0	16 (37)	45 (52)	81 (53)	1097 (55)	0.073 **
N1	8 (19)	21 (24)	37 (24)	484 (24)	0.833 **
N2	16 (37)	16 (18)	24 (16)	263 (13)	0.001 **
Not given	5 (11)	5 (6)	11 (7)	154 (8)	
Dukes' stage					
A	9 (20)	16 (18)	41 (27)	443 (22)	0.451 **
B	7 (16)	24 (28)	36 (24)	588 (29)	0.092 **
C	11 (24)	24 (28)	43 (28)	542 (27)	0.971 **
D	17 (38)	21 (24)	28 (18)	385 (19)	0.019 **
Not given	1 (2)	2 (2)	5 (3)	40 (2)	

Between the Age Groups*

Fisher Exact **

Oneway Anova***

Table 2 Characteristics of 1354 Patients under 70 Years of Age treated with Curative AR or APR and TME Technique

	< 40 years	40 - 44 years	45 - 49 years	50 - 69 years	P*
	n (%)	n (%)	n (%)	n (%)	
Total number treated	18 (1)	54 (4)	92 (7)	1190 (88)	
Age, mean(range)	34(18-39)	43(40-44)	48(45-49)	62(50-69)	
Gender					< 0.001**
Female	13 (72)	34 (63)	41 (45)	473 (40)	
Male	5 (28)	20 (37)	51 (55)	717 (60)	
Lower border (cm), mean(range)	9.0(3-15)	8.7(1-16)	8.2(0-16)	8.8(0-16)	0.682***
Operative treatment					0.459**
AR	15 (83)	37 (69)	63 (69)	875 (73)	
APR	3 (17)	17 (32)	29 (32)	315 (27)	
Tumor diameter (cm), mean(range)	4.7(0-9)	4.4(1-10)	4.4(1-8)	4.4(0-12)	0.846***
Differentiation					
G1 (well)	1 (6)	4 (7)	10 (11)	96 (8)	0.783**
G2 (medium)	12 (67)	39 (72)	70 (76)	903 (76)	0.702**
G3 (poor)	4 (22)	10 (19)	6 (7)	118 (10)	0.039**
Not given	1 (6)	1 (2)	6 (7)	73 (6)	
T-stage					
T1	1 (6)	10 (19)	8 (9)	106 (9)	0.138**
T2	6 (33)	9 (17)	33 (36)	306 (26)	0.055**
T3	9 (50)	29 (54)	43 (47)	681 (57)	0.230**
T4	2 (11)	6 (11)	8 (9)	97 (8)	0.689**
Not given	0 (0)	0 (0)	0 (0)	0 (0)	
N-stage					
N0	10 (56)	33 (61)	54 (59)	779 (66)	0.416**
N1	4 (22)	13 (24)	28 (30)	280 (24)	0.510**
N2	4 (22)	8 (15)	10 (11)	130 (11)	0.324**
Not given	0 (0)	0 (0)	0 (0)	1 (0)	
Dukes' stage					
A	5 (28)	14 (26)	30 (33)	343 (29)	0.844**
B	5 (28)	19 (35)	24 (26)	436 (37)	0.202**
C	8 (44)	21 (39)	38 (41)	410 (35)	0.404**
Not given	0 (0)	0 (0)	0 (0)	1 (0)	
R-stage					0.853**
R0	17 (94)	49 (91)	87 (95)	1105 (93)	
R1	1 (6)	5 (9)	5 (5)	85 (7)	
Preoperative radiotherapy					0.984**
Yes	1 (6)	3 (6)	6 (7)	72 (6)	
No	17 (94)	51 (94)	86 (94)	1118 (94)	
Postoperative radiotherapy					0.021**
Yes	4 (22)	6 (11)	7 (8)	69 (9)	
No	14 (78)	48 (89)	85 (92)	1121 (94)	
Postoperative mortality (30 days)					0.854**
Yes	0 (0)	0 (0)	0 (0)	17 (1)	
No	18 (100)	54 (100)	92 (100)	1173 (99)	

Between the Age Groups *

Fisher Exact **

Oneway Anova***

AR = anterior resection

**Table 3 Five-year Overall Survival According to Age Group,
2283 Patients under 70 years of Age with Rectal Cancer**

Age Group	No of Patients n	Overall Survival	
		%	95% CI* p = 0.004**
< 40 years	45	38	23 - 54
40 - 44 years	87	70	60 - 80
45 - 49 years	153	62	53 - 71
50 - 70 years	1998	56	53 - 58
Total	2283	56	54 - 59

* Kaplan-Meier, ** log rank test

Table 4 Five-year Local Recurrence, Metastasis, Overall Survival and According to Age Group, 1354 Patients under 70 years of Age treated with Curative AR or APR and TME technique for Rectal Cancer

Age Group	No of Patients n	Local Recurrence		Metastasis		Overall Survival	
		%	95% CI* p = 0.264**	%	95% CI* p = 0.003**	%	95% CI* p = 0.029**
< 40 years	18	20	0 - 41	56	33 - 79	54	27 - 81
40 - 44 years	54	8	0 - 18	22	11 - 34	88	79 - 97
45 - 49 years	92	18	9 - 26	20	11 - 28	76	66 - 86
50 - 70 years	1190	14	12 - 16	26	24 - 29	71	68 - 74
Total	1354	14	12 - 16	26	23 - 28	72	69 - 75

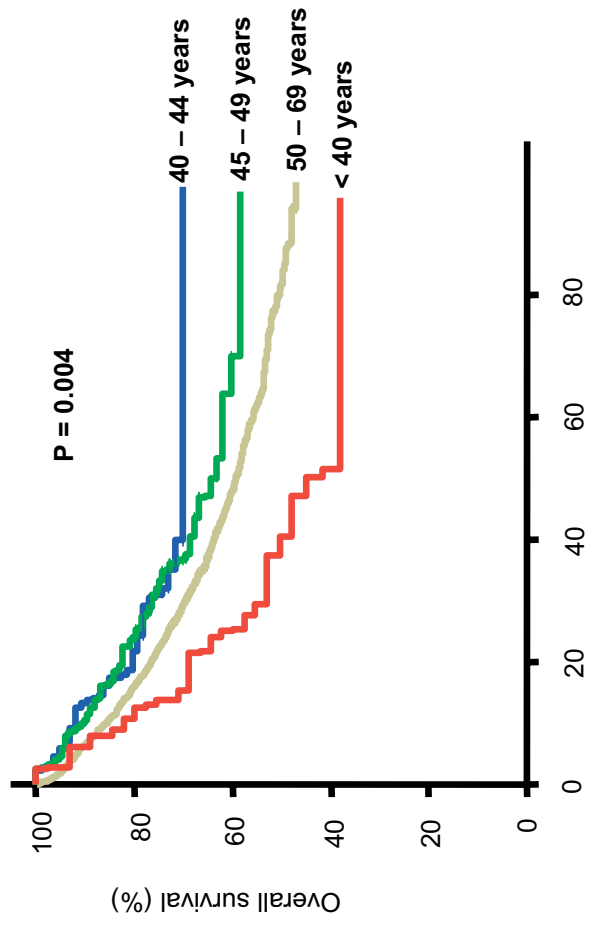
* Kaplan-Meier, ** log rank test
AR = anterior resection

Table 5 Factors influencing Local Recurrence, Overall Survival and Metastasis after Curative APR/AR with TME Technique in 1354 Patients with Rectal Cancer

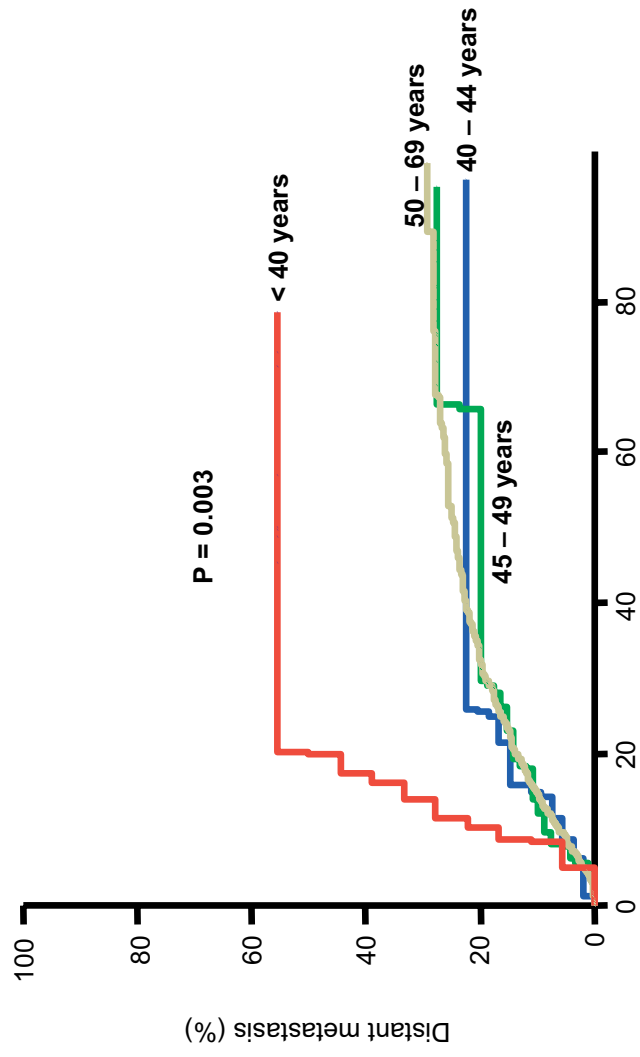
Variable	Local Recurrence			Metastasis			Overall Survival		
	HR	95% CI	P*	HR	95% CI	P*	HR	95% CI	P*
Gender			0.043			0.030			< 0.001
Female	1	Reference		1	Reference		1	Reference	
Male	1.4	1.0 - 2.0		1.3	1.0 - 1.7		1.5	1.2 - 1.9	
Age group			0.181			< 0.001			0.012
40 - 44	1	Reference		1	Reference		1	Reference	
< 40	5.7	1.0 - 34.3		5.1	2.1 - 12.0		6.2	2.0 - 19.7	
45 -49	4.8	1.1 - 21.1		1.1	0.5 - 2.3		2.5	0.9 - 6.9	
50 -69	3.7	0.9 - 14.8		1.2	0.7 - 2.2		3.3	1.4 - 8.0	
T - Stage			0.003			< 0.001			< 0.001
T1	1	Reference		1	Reference		1	Reference	
T2	1.5	0.6 - 4.0		1.0	0.5 - 2.2		0.9	0.5 - 1.7	
T3	2.6	1.0 - 6.4		3.1	1.5 - 6.3		2.1	1.1 - 3.8	
T4	4.0	1.5 - 10.7		5.2	2.4 - 11.1		5.0	2.6 - 9.4	
N - stage			< 0.001			< 0.001			< 0.001
N0	1	Reference		1	Reference		1	Reference	
N1	1.8	1.2 - 2.5		2.0	1.5 - 2.6		1.6	1.2 - 2.0	
N2	2.6	1.7 - 4.0		3.7	2.8 - 5.0		2.9	2.2 - 3.9	
Differentiation			0.860			0.293			0.002
Well/Medium	1	Reference		1	Reference		1	Reference	
Poor	1.0	0.6 - 1.7		1.2	0.9 - 1.6		1.6	1.2 - 2.1	

AR = anterior resection; APR = abdominoperineal resection; TME = total mesorectal excision; HR = hazard ratio; CI = confidence interval

* Cox regression



Numbers at risk					
	45	31	19	10	3
< 40 years	45	31	19	10	3
40 - 44 years	87	70	44	29	15
45 - 49 years	153	126	78	39	20
50 - 69 years	1998	1530	985	552	254



Numbers at risk	0	10	20	30	40	50	60	70	80
< 40 years	18	10	8	3	0				
40 - 44 years	54	46	33	20	11				
45 - 49 years	92	78	52	25	11				
50 - 69 years	1190	978	642	357	168				

