

available at www.sciencedirect.comjournal homepage: www.ejconline.com

Survival of elderly rectal cancer patients not improved: Analysis of population based data on the impact of TME surgery

Harm Rutten^{a,*}, Marcel den Dulk^b, Valery Lemmens^c, Grard Nieuwenhuijzen^a, Pieta Krijnen^d, Marlies Jansen-Landheer^d, Lonneke van de Poll Franse^c, Jan-Willen Coebergh^c, Hendrik Martijn^e, Corrie Marijnen^f, Cock van de Velde^b

^aDepartment of Surgery, Catharina Hospital, Michelangelolaan 2, PO Box 1350, 5623 ZA Eindhoven, The Netherlands

^bDepartment of Surgery, Leiden University Medical Centre, The Netherlands

^cComprehensive Cancer Centre South, Eindhoven, The Netherlands

^dComprehensive Cancer Centre West, Leiden, The Netherlands

^eDepartment of Radiotherapy, Catharina Hospital, Eindhoven, The Netherlands

^fDepartment of Radiotherapy, Leiden University Medical Centre, The Netherlands

ARTICLE INFO

Article history:

Received 14 May 2007

Received in revised form 1 July 2007

Accepted 10 July 2007

Available online 20 August 2007

Keywords:

Rectal cancer

Survival

Elderly

Aged

Population based

ABSTRACT

Introduction: The incidence of rectal cancer is highest in elderly patients. However, these patients are often underrepresented in randomised studies. Therefore, it is not clear whether results of rectal cancer studies are equally applicable to both elderly and younger patients.

In this paper, the Dutch Total Mesorectal Excision (TME) study is revisited, focused on patients aged 75 years and above. The rectal cancer databases of the Comprehensive Cancer Centres (CCC) South and West were combined to analyse the effect of the TME-study in three different periods: before (1990–1995), during (1996–1999) and after (2000–2002) the trial.

Results: Implementation of preoperative radiotherapy, as investigated in the TME trial, and the introduction of TME surgery resulted in improved 5 year survival during the subsequent periods, in patients younger than 75 years, of 60% (1990–1995) to 67% (1996–1999) and 70% (2000–2002) (log rank $p < 0.0001$). The older patients did not improve and remained at 41%, 40% and 43% at 5 years in the respective periods.

Furthermore, mortality during the first 6-month period after treatment is significantly raised compared to younger patients: 14% in the elderly, compared to 3.9% in the younger TME-study patient ($p < 0.0001$ χ^2). In the CCC database these figures were confirmed at 16% and 3.9% ($p < 0.0001$ χ^2).

Conclusion: Overall survival was not improved in the elderly rectal cancer patient after introduction of preoperative radiotherapy and TME-surgery. Non-cancer related mortality is a significant problem in the first 6 months after surgery.

© 2007 Elsevier Ltd. All rights reserved.

* Corresponding author.

E-mail address: harm.rutten@cze.nl (H. Rutten).

0959-8049/\$ - see front matter © 2007 Elsevier Ltd. All rights reserved.

doi:10.1016/j.ejca.2007.07.009

1. Introduction

Few data are available about the proper treatment of elderly patients with rectal cancer. The median age of patients that are enrolled in rectal cancer studies is around the mid-60s. Often patients are excluded either because they are too old: i.e. older than 75 years, or they are excluded as a result of co-morbidity or high ASA (American Society of Anaesthesiology) classification. Despite the fact that surgery is the only proven curable treatment for rectal cancer there are no randomised studies focusing on the improvement of rectal cancer surgery in the elderly. The introduction of TME (Total Mesorectal Excision) surgery has led to a major decrease of the local recurrence rate and an improvement in survival rate.^{1,2} TME surgery is an explicit improvement of the quality of surgery and therefore not suitable to be investigated in randomised trials: it is impossible to compare 'good' surgery with 'bad' surgery in a randomised fashion. In the Netherlands, a randomised study comparing TME surgery alone to TME surgery preceded by 5 times 5 Gray short course of radiotherapy led to the introduction of this new technique.³ This introduction happened almost instantaneously in 1996; within 6 months, surgeons in 80 Dutch hospitals were trained through workshops and the attendance of a referent surgeon at the first five procedures. This relative short transition period to TME surgery creates the opportunity to study population based databases from the Comprehensive Cancer Centres (CCC) South (Eindhoven Cancer Registry) and West in periods before, during and after introduction of TME surgery. The findings of the randomised study can be correlated with the population based databases. In the CCC databases all older patients are included. Therefore, it was a challenge to research if findings from the TME study permeated equally into the younger and older rectal cancer population.

The authors of this paper were involved in accumulating data of rectal cancer treatment without the exclusion of older patients: the first database being used is the combined population-based database of two comprehensive cancer centres (South and West) in the Netherlands; the second is the database from the Dutch TME-study.

Several questions have to be answered. The most important question remains whether it is reasonable to apply the guidelines based on relatively younger patients to the elderly. Secondary questions are: do the same risk-factors apply to the elderly and do subsequent adjuvant treatments yield the same response? And lastly, must special circumstances be taken into account?

2. Patients and methods

Data were derived from the cancer registry of the population-based Comprehensive Cancer Centres (CCC) South and West. Registration is based on notification of all newly diagnosed malignancies after which data is obtained from clinical records in hospitals. The Dutch regional Cancer Registries have been shown to attain a completeness of data exceeding 95%.⁴ Patients that underwent a resection for cancer located in the rectum (International Classifications of

Diseases-9 154.1) and diagnosed between January 1990 and December 2002 were selected for analysis. Patients with prior invasive adenocarcinoma or with distant metastases diagnosed prior to or during surgery were discarded, as well as patients who underwent polypectomy or transanal endoscopic microsurgery.

The period of study was divided into three periods: 1990–1995 (pre-trial period), 1996–1999 (trial period) and 2000–2002 (post-trial period). Age was categorised into younger than 75 years and 75 years or older. A total number of 4567 patients, of which 28% were 75 years or older, was included. Data on tumour stage and data on preoperative RT were also obtained from the cancer registries. Survival data were obtained from hospitals, general practitioners and the Central Bureau for Genealogy, which registers all deceased persons in the Netherlands.

The other dataset used came from the Dutch TME study. From January 1996 until December 2000, 1861 patients were randomly assigned to either preoperative radiotherapy (5 × 5 Gy) followed by TME or TME alone in a large, international, multicentre trial (3). Details of the TME study have been described elsewhere.^{5,6} All patients were required to give informed consent before randomisation. Only Dutch patients (*n* = 1530) were considered in the present analysis because collection and verification of data were, for logistical reasons, feasible for these patients only. Patients with concomitant metastases or who were not resected were excluded. For the underlying study, 1356 patients were selected. Of all the patients in this database, 230 were 75 years or older (17%).

2.1. Statistical analysis

Data were analysed with the SPSS package (SPSS 15.0 for Windows; SPSS Inc, Chicago, IL). Univariate comparisons of categorical variables were performed by a χ^2 test. Preoperative treatment, gender, distance, TNM-stage, type of resection, preoperative complications, postoperative infectious, general or surgical complications were first univariately analysed for their association with hospital mortality, defined as mortality during the admission in which the TME procedure was performed, and 180-day mortality. All variables with a *p*-value of ≤ 0.10 were tested in a multivariate logistic regression analysis. Kaplan–Meier curves for overall survival of patients were compared using the log-rank test. All survival data are presented at 5 years. Two-sided *p*-values ≤ 0.05 were considered statistically significant.

Prognostic groups were created based on significant variables and analysed and presented using a Cox regression survival model.

3. Results

The combined database of the Comprehensive Cancer Centres South and West showed that survival of rectal cancer patients has improved over time. These data will be described elsewhere in greater detail (personal communication, M. den Dulk, Leiden University Medical Centre). Interestingly, this improvement was observed in patients younger than 75 years (Fig. 1). For younger patients, TME-surgery and preoperative

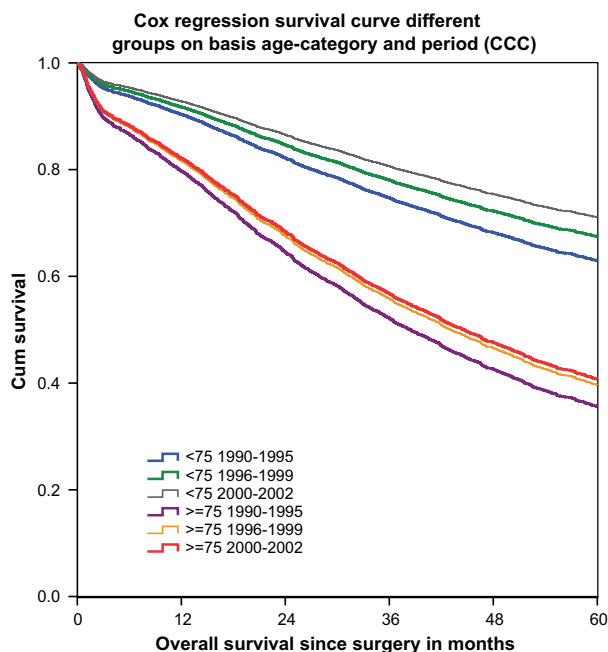


Fig. 1 – Cox regression overall survival curves in the CCC combined database Improved survival over the subsequent periods in the younger patients ($p < 0.0001$), but no improvement in the subsequent periods for the elderly patients.

radiotherapy were introduced in the second observation period (1996–1999) in the frame of a randomised study, which led to a significant decrease of the hazard ratio to 0.81, and rise of the 5-year survival rate from 60% in the first period to 67% in the second period. After general introduction of TME-surgery and 5×5 preoperative radiotherapy, the expected survival rate of younger patients increased to 70% and the relative risk decreased further to 0.70 when compared to the first period ($p < 0.0001$). For the elderly rectal cancer patient, the expected 5-year survival rate was 41% in the first period, but it remained 40% and 43% in the respective second and third periods. Compared to people of the same age from the general population, the relative risk of dying from rectal cancer increased 5.2 times in younger and 1.6 times in older patients (data not shown). In the Dutch population, men and women still have a life expectancy of 5 years at the ages of 84 and 87 respectively (Central Bureau of Statistics: www.statline.cbs.nl).

The proportion of patients receiving preoperative radiotherapy in the TME study did not differ between the younger and elderly (younger <75 years 50% radiotherapy plus TME versus 49% in the elderly, $p = 0.70$). Sex distribution did differ between the age groups: in the younger patients, 65% were male compared to 56% in the elderly ($p = 0.006$). More sphincter conserving procedures were performed in the younger, 66% versus 60% in the elderly ($p < 0.001$). TNM-stage distribution also differed: in the young 27% stage 2 and 39% stage 3 whereas in the elderly these figures were 35% and 33% respectively ($p = 0.021$). T-stage distribution differed slightly: 6.0% T1, 34% T2, and 55% T3 in the younger patients versus 2.6%, 33%, and 59% in the elderly ($p = 0.038$). N-stage did not differ

between age groups. No patients in this study had metastatic disease. Therefore, mortality during the first month or first 6 months cannot be contributed to cancer progression, but is rather treatment-related. During the first month, the elderly had a significant higher mortality rate, 7.8% versus 2.5% ($p < 0.0001$). However, this difference exaggerates in the ensuing months. The six-month mortality rate for the elderly was 14% versus 3.3% for the younger patients ($p < 0.0001$). In the TME plus preoperative radiotherapy arm, the 6-month mortality rate for the elderly was 17% compared to 12% in the surgery-alone arm; these figures do not reach statistical significance ($p = 0.27$).

The six-month mortality rate was also significantly raised in the CCC database: 16% for age 75 and above and 3.9% in the younger patients. For 1-month mortality, these figures were 4.5% and 0.8% respectively. Six-month mortality rates did not decline during the study period. These figures are lower than in the TME study, because the primary date is the date of diagnosis and not the date of surgery, which was unfortunately not recorded in the CCC registries. For the elderly, 6 month-mortality was 15%, 18%, and 16% in the consecutive periods. For the younger patients, these figures were 3.9%, 4.1% and 3.6%. No influence on 6-month mortality was found with regard to TNM, T-stage, N-stage, preoperative versus no radiotherapy or type of surgical procedure. Interestingly, those older patients who received postoperative radiotherapy experienced significantly less 6-month mortality, despite the fact that their overall survival was the worst: 37% (postoperative radiotherapy), 40% (no radiotherapy at all) and 48% (preoperative radiotherapy). In younger patients, similar findings were encountered: 6-month mortality was 5.1%, 3.3% and 1.4% ($p < 0.0001$) for no radiotherapy, preoperative radiotherapy and postoperative radiotherapy respectively. Again, an inverse relation with overall survival was noticed: 68%, 68%, and 53% ($p < 0.0001$) for no, preoperative and postoperative radiotherapy.

In the Dutch TME-study, patients aged 75 years and older showed a better response in the study arm when compared to younger patients. Younger patients have a significantly lower local recurrence rate of 5.2% after preoperative 5×5 Gy radiotherapy versus 11% for patients without preoperative radiotherapy ($p = 0.001$). However, overall survival at 5 years (respectively 72% and 72%, $p = 0.30$), distant metastases free survival (74% versus 72%, $p = 0.70$) and cancer-free survival (81% versus 78%, $p = 0.44$) were not improved. Whereas in the elderly, apart from local recurrence rate (5.4% versus 14%, $p = 0.02$), also distant metastases free survival (81% versus 69%, $p = 0.07$) and cancer-free survival (81% versus 66%, $p = 0.03$) were improved. The 5-year overall survival rate in the elderly (48% versus 43%, $p = 0.27$), much like in the younger patients, was only slightly improved in the study arm that received 5×5 Gy preoperative radiotherapy (Figs. 2 and 3).

Complications occurred more frequently in older patients: any postoperative (infectious, general or surgical) complication occurred in 42% of patients aged younger than 75 years compared with 51% in older patients ($p = 0.008$). Pulmonary, renal, neurological, thrombo-embolism, cardiac, hypertension, line sepsis, and cholecystitis were scored as general complications. Wound infection, abscess, sepsis/febris eci, and haematoma were the infectious complications, and

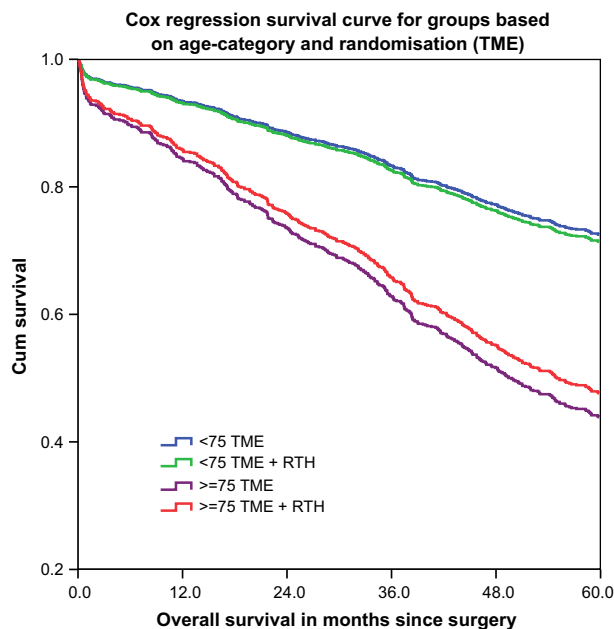


Fig. 2 – Cox regression overall survival curve in the TME study. A significant increase of the risk of dying for the elderly ($p < 0.0001$), but randomisation within the same age-category was of no influence.

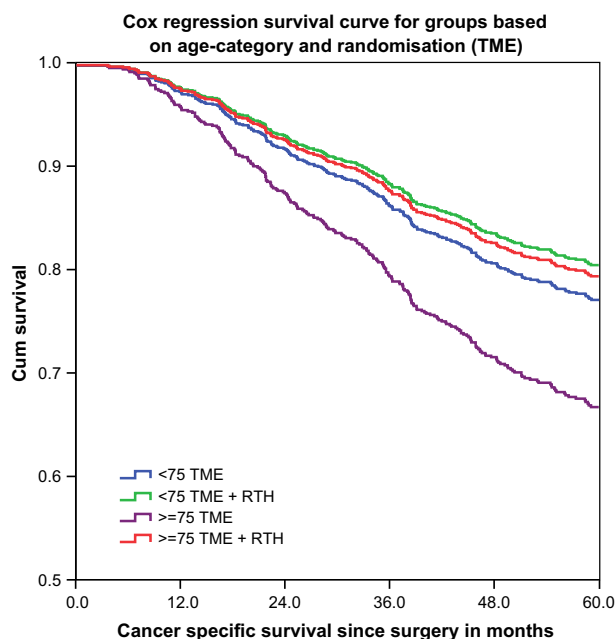


Fig. 3 – Cox regression survival curve of cancer specific survival in the TME study. Cancer specific survival was significantly decreased in the elderly, not receiving preoperative radiotherapy ($p < 0.045$, HR 1.76). No difference among the other three groups.

abdominal wound dehiscence, perineal wound dehiscence, intestinal necrosis, ileus, leakage, bleeding, fistula, stoma complications, perforation were considered surgical compli-

cations. Six-month mortality was significantly influenced by general (Odds ratio (OR) = 3.74, $p = 0.002$) and surgical postoperative complications (OR = 4.93, $p < 0.001$). Radiotherapy, sex, distance, TNM-stage and perioperative complications were not independent contributors. Type of surgical resection was borderline significant ($p = 0.059$). Besides, infectious postoperative complications were not associated with 6 months mortality.

Complications had a greater impact among elderly patients compared to younger patients, i.e. if an anastomotic leakage occurs, the probability of fatal outcome is 50.0% compared to 7.1% in younger patients ($p < 0.001$). However, the overall occurrence of anastomotic leakage is not increased in the elderly: 10% in the elderly compared to 12% in the younger ($p = 0.63$, low anterior resected patients only).

4. Discussion

From the population-based registries of the Comprehensive Cancer Centre South and Comprehensive Cancer Centre West it is evident that the prognosis of patients with rectal cancer has improved over the last 15 years.⁷ In Sweden, having the same history of introducing 5×5 Gy preoperative radiotherapy and TME-surgery, these findings were also made.⁸ The major change in the treatment of rectal cancer was the introduction of TME-surgery and the introduction of 5×5 Gy preoperative radiotherapy for stage 2 and stage 3 rectal cancers. From the registry-based results, it is also obvious that younger patients have benefited more from the change in cancer treatment than the 75 years and older patients. There is a very evident paradox, as it seems that from the results of the Dutch TME-study it can be concluded that the biological behaviour of rectal cancer in the elderly in response to treatment is better than in younger patients. Not only is local recurrence rate decreased by the addition of 5×5 Gy preoperative radiotherapy, but also the distant metastatic rate and the cancer specific survival. Unfortunately, this favourable responsiveness comes with a price. The impact of complications in the elderly is more severe. However, neoadjuvant treatment does not lead to statistically significant more complications in the elderly, but this may be due to a power effect. The elderly are a small group within the Dutch TME-study and in the whole group of patients treated in the Dutch TME-study neoadjuvant treatment did lead to more complications.⁹ In the elderly, complications more often have a fatal course. Significant mortality occurs not only during stay in hospital, but is present until 6 months after surgery. Even in the Dutch TME-study where elderly patients constitute a highly selected group of patients fit enough to undergo treatment, approximately one out of six will die within 6 months after the treatment.

In the combined CCC database, 6-month mortality was equally high in all periods around 16%, indicating that the changes in therapeutical approach had little impact, and that the surgical trauma by itself, being non-TME or TME, is the most important factor for postoperative mortality. In the general rectal cancer population, the elderly suffer

more often from multiple comorbidity, which cause more complications during treatment.¹⁰ Elderly were underrepresented in the Dutch TME-study. Age was no exclusion criterion but poor performance status was, and most elderly suffer from comorbidity, influencing performance status. From previous epidemiological studies it is known that older people are less likely to receive adjuvant or neoadjuvant treatment. When elderly are not considered to receive adjuvant or neoadjuvant treatment, they are considered even less for participation in a study investigating (neo-)adjuvant treatment.

Rectal cancer is a disease of the elderly. The chance of developing a rectal cancer increases with age and is highest at the age of 80.¹¹ The fact that survival did not improve in the older rectal cancer patients casts some doubt as to whether the approach to rectal cancer in the elderly should be the same as in younger patients. Despite the fact that older patients respond very well to neoadjuvant treatment, the intercurrent mortality not related to cancer obscures any beneficial effect. In the elderly, not only is cancer-related mortality an outcome parameter, but also mortality which is not cancer-related. The relative risk of dying from rectal cancer is 1.6 in the elderly compared to 5.2 in younger patients. Therefore, it can be argued that the focus of treatment should be on preventing non-cancer-related mortality.

Theoretically, two approaches can be followed to achieve reduction of mortality. The first is to optimise the condition of the patient; making him or her more fit for the operation. This approach requires thorough preoperative assessment of amongst others the nutritional, metabolic, cardiac, and pulmonary status of the patient. Standardising risk assessments by the routine use of scorings systems like the P-possum may be a step forward.^{12,13} However, this is beyond the scope of this article. The other approach is to reduce the risk or the toxicity of the treatment. This does not mean that a palliative treatment instead of a curative treatment should be offered. If the life expectancy exceeds 1 year, an initially palliative treatment will lead to death from progressive rectal cancer. Moreover, radiotherapy without surgery in potentially curative patients limits the palliative options in case of local progression and secondary curative surgery will certainly be more hazardous. Therefore, curative treatment is the better option.

Combined treatment is more effective than surgery alone, but also carries greater risks. Heald, who has published his excellent personal series, argues that in patients with perfect mesorectal excision, preoperative radiotherapy may be omitted.¹⁴ However, results from the CRO7 study show that even in perfect surgery there is added value of preoperative radiotherapy.¹⁵ An ongoing Scandinavian study investigates the effect of delaying surgery after a short course of radiotherapy.¹⁶ The study goal is to see whether delay leads to downsizing and staging for the tumour. Other effects could be that after a waiting period of 6–12 weeks, the patient recovers from the radiotherapy and avoids the double jeopardy of radiotherapy and a major surgical trauma. Nutritional, metabolic, cardiac, or pulmonary disorders may be optimised in the waiting period.

The surgical approach must also be tailored to the patient. The keywords are optimisation of the patient and individualisation of the treatment to the patient. One of the most feared and life-threatening complications can be avoided by not

restoring the continuity of the bowel. However, anastomotic leakage does not occur more often in the elderly.¹⁷ The subsequent complications of anastomotic failure are more serious. Postoperative mortality after complications is substantially higher among the elderly. In addition, this increased mortality persists at least for the first 6 months after surgery.

Apart from a risk factor for recovery, restoration of continuity requires secondary surgery (closure of the temporary colostomy or ileostomy) with its implicit morbidity. Removal of the rectal ampulla and replacing it with the low anterior anastomosis results in a serious handicap. Most patients will experience a longer period of increased frequency, urge, soiling, fragmented and less solid defecation.^{18–20} This often leads to incontinence and, subsequently, more dependency for care and inclination to social isolation. In a period of life with less mobility, loss of relatives and friends, threats of social isolation must be taken very seriously. Despite this fear, the TME study did not provide data that older patients more often experience worse incontinence than younger ones. At least with regard to the number of patients aged 75 years and older included in the TME study, the 10% difference in worse incontinence did not reach statistical significance.²¹ The only finding in the elderly that reached statistical difference was the fact that 21% of the elderly versus 8% of the younger patients had no reversal of their temporary stoma.²²

The role of local excision after neoadjuvant treatment or even treatment solely with radiochemotherapy and omitting surgery has not been explored. The elderly patient, especially, is a good candidate for these sorts of studies that focus on reducing the surgical trauma.²³

5. Conclusion

The paradox in the treatment of rectal cancer in elderly patients is that the treatment is even more effective than in younger patients, but that overall survival is obscured by an increase in non-cancer-related mortality. Improvement of outcome in elderly patients can be realised if non-cancer-related mortality is reduced. This objective can be realised by optimising the condition of the patient or by reducing the toxicity of the treatment. Ideally, randomised studies for elderly patients should be performed. Extrapolation of results of younger patients may not be appropriate. Postoperative or post-treatment mortality should be recorded for at least up to 6 months after the primary treatment. The (in-)capacities to take care of themselves and the social environment must bear more weight than the technical possibilities in proposing certain surgical procedures.

Conflict of interest statement

None declared.

Acknowledgement

MdD and CvdV have been supported by a Quality Assurance Fellowship from the European Society of Surgical Oncology.

REFERENCES

1. Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978–1997. *Arch Surg* 1998;**133**(8):894–9.
2. Kapiteijn E, Putter H, van de Velde CJ. Impact of the introduction and training of total mesorectal excision on recurrence and survival in rectal cancer in The Netherlands. *Br J Surg* 2002;**89**(9):1142–9.
3. Kapiteijn E, Kranenbarg EK, Steup WH, et al. Total mesorectal excision (TME) with or without preoperative radiotherapy in the treatment of primary rectal cancer. Prospective randomised trial with standard operative and histopathological techniques. Dutch ColoRectal Cancer Group. *Eur J Surg* 1999;**165**(5):410–20.
4. Schouten LJ, Hoppener P, van den Brandt PA, Knottnerus JA, Jager JJ. Completeness of cancer registration in Limburg, The Netherlands. *Int J Epidemiol* 1993;**22**(3):369–76.
5. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *New Engl J Med* 2001;**345**(9):638–46.
6. Peeters KC, Marijnen CA, Nagtegaal ID, et al. The randomized controlled TME trial after a median follow up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. *Ann Surg* 2007 [in press].
7. Martijn H, Voogd AC, van de Poll-Franse LV, Repelaer van Driel HJ, Rutten HJ, Coebergh JW. Improved survival of patients with rectal cancer since 1980: a population-based study. *Eur J Cancer* 2003;**39**(14):2073–9.
8. Birgisson H, Talback M, Gunnarsson U, Pahlman L, Glimelius B. Improved survival in cancer of the colon and rectum in Sweden. *Eur J Surg Oncol* 2005;**31**(8):845–53.
9. Marijnen CA, Kapiteijn E, van de Velde CJ, et al. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial. *J Clin Oncol* 2002;**20**(3):817–25.
10. Shahir MA, Lemmens VE, van de Poll-Franse LV, Voogd AC, Martijn H, Janssen-Heijnen ML. Elderly patients with rectal cancer have a higher risk of treatment-related complications and a poorer prognosis than younger patients: a population-based study. *Eur J Cancer* 2006;**42**(17):3015–21.
11. http://www.ikcnet.nl/system/image_viewer/index.php.
12. Wakabayashi H, Sano T, Yachida S, Okano K, Izuishi K, Suzuki Y. Validation of risk assessment scoring systems for an audit of elective surgery for gastrointestinal cancer in elderly patients. *Int J Surg* 2007. epub.
13. Ferjani AM, Griffin D, Stallard N, Wong LS. A newly devised scoring system for prediction of mortality in patients with colorectal cancer: a prospective study. *Lancet Oncol* 2007;**8**(4):317–22.
14. Hermanek P, Heald RJ. Pre-operative radiotherapy for rectal carcinoma? Has the case really been made for short course pre-operative radiotherapy if surgical standards for rectal carcinoma are optimal? *Colorectal Dis* 2004;**6**(1):10–4.
15. Quirke P, Sebag-Montefiore D, Steele R, et al. Local recurrence after rectal cancer resection is strongly related to the plane of surgical dissection and is further reduced by preoperative short course radiotherapy. Preliminary results of the MRC CR07 trial. *J Clin Oncol* 2006;**24**:A3512.
16. Glimelius B. Rectal cancer irradiation Long course, short course or something else? *Acta oncol (Stockholm, Sweden)* 2006;**45**(8):1013–7.
17. Peeters KC, Tollenaar RA, Marijnen CA, et al. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. *Br J Surg* 2005;**92**(2):211–6.
18. Marijnen CA, van de Velde CJ, Putter H, et al. Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: report of a multicenter randomized trial. *J Clin Oncol* 2005;**23**(9):1847–58.
19. Peeters KC, van de Velde CJ, Leer JW, et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients—a Dutch colorectal cancer group study. *J Clin Oncol* 2005;**23**(25):6199–206.
20. Phillips PS, Farquharson SM, Sexton R, Heald RJ, Moran BJ. Rectal cancer in the elderly: patients' perception of bowel control after restorative surgery. *Dis colon rectum* 2004;**47**(3):287–90.
21. Lange MM, den Dulk M, Bossema ER, Maas CP, et al. Cooperative clinical investigators of the TME-trial. Risk factors for faecal incontinence after rectal cancer treatment. *Br J Surg* 2007 [in press].
22. den Dulk M, Smit M, Peeters KC, et al. A multivariate analysis of limiting factors for stoma reversal in patients with rectal cancer entered into the total mesorectal excision (TME) trial: a retrospective study. *Lancet Oncol* 2007;**8**(4):297–303.
23. Habr-Gama A, Perez RO, Proscurshim I, et al. Patterns of failure and survival for nonoperative treatment of stage c0 distal rectal cancer following neoadjuvant chemoradiation therapy. *J Gastrointest Surg* 2006;**10**(10):1319–28; discussion 1328–1319.