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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

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ABSTRACT

Objective: To document local recurrence in primary rectal cancer when standardised techniques of surgery, radiotherapy, and pathology are used, and to investigate whether the local recurrence rate after total mesorectal excision permits the omission of adjuvant short term preoperative radiotherapy.

Design: Prospective randomised study.

Setting: Dutch ($n = 80$), English ($n = 1$), German ($n = 1$), Swedish ($n = 9$), and Swiss ($n = 1$) hospitals.

Subjects: The first 500 randomised Dutch patients with primary rectal cancer.

Main outcome measures: Local recurrence, survival, operation-related factors, specific pathological tumour characteristics, short and long term morbidity, and quality of life.

Results: Between January 1996 and April 1998, 871 Dutch and 94 other patients were randomised. Our feasibility analysis shows that cooperation between and within the participating disciplines goes well. With regard to the surgical part, this can be confirmed by the large number of operations attended by consultant surgeons (58%). The number of abdominoperineal resections appeared to be low (30%), as did the percentage of lateral margins involved (13%). The rate of adverse effects of radiotherapy was acceptable. Apart from a larger operative blood loss and a higher infective complication rate in the irradiated group, no significant differences were found with regard to morbidity and mortality between the randomised groups.

Conclusions: The accrual of our trial is going well and it is feasible; short term preoperative radiotherapy is safe even in combination with TME.

Key words: prospective randomised study, primary rectal cancer, TME-surgery, preoperative radiotherapy.

INTRODUCTION

One of the main problems in the treatment of rectal cancer is the development of local recurrences. These cause severe disabling symptoms, are difficult to treat, and usually kill the patient (33). Recurrences of rectal cancer are often confined to the pelvis without distant metastases, and are considered locoregional failures (1, 11). Most of them become overt within two years of operation and the reported incidence varies widely from 5%–45% (8, 16). Studies in three Comprehensive Cancer Centres in The Netherlands showed recurrence rates of 18% (4), 22.5% (13), and 18% (20).

The conventional procedure usually implies partially blunt dissection of the rectum along the presacral fascia, more distally directed "cone-wise" towards the rectal wall to allow for a low anastomosis. This procedure results in incomplete removal of mesorectal tissue, with a high risk of local failure and damage to the autonomic pelvic nerve plexus with a resulting high incidence of sexual (9, 32) and bladder dysfunction (24). Surgeons who have specialised in rectal surgery have better results in terms of improved local control and survival, and less morbidity. Heald and Karanjia (10) and Enker (5) advocate the concept of circumferential or total mesorectal excision (TME). Moriya et al. (21) routinely do an extended lateral pelvic lymph node dissection.

Several studies have suggested that radiotherapy may be of benefit in the treatment of rectal cancer.

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Given both preoperatively and postoperatively it has been shown to improve local control and disease-free survival (6, 17, 30). In a large, prospective, Swedish trial preoperative hypofractioned radiotherapy resulted in better local control than postoperative radiotherapy (23). Recent results of the Swedish Rectal Cancer Trial have showed reduced local recurrence rates and improved overall survival with the short term preoperative 5 Gy $\times$ 5 regimen compared with surgery alone (31).

The role of chemotherapy in the treatment of primary rectal cancer still has to be defined. In the United States the opinion is that all patients with Dukes B or C lesions should have postoperative chemoradiotherapy (National Cancer Institute, USA. Clinical announcement: adjuvant therapy for rectal cancer. 14 March 1991, 14). This is not routine in Europe, where chemotherapy is still considered investigational treatment for rectal cancer.

However, a major problem of all published trials on adjuvant therapy in the treatment of primary rectal cancer is that the surgery has not been standardised. The surgeon remains an important factor in controlling the tumour and reducing morbidity (22). So, the effect of adjuvant therapy can be studied only when the surgical technique is strictly standardised and quality-controlled.

Optimal quality control of the operation must also include a standardised examination by pathologists (26, 27). Detection of mesorectal spread requires systematic examination of the specimen by serial sectioning of the whole tumour and the surrounding mesorectum in the transverse plane. This method can be used to monitor differences in operative technique.

These considerations led us to set up a trial in rectal cancer patients in which TME and pathology are standardised, in which randomisation takes place for preoperative radiotherapy, and in which strict quality control is undertaken for the surgical, radiotherapeutic, and pathological disciplines. The study objectives are to document local control of disease in primary rectal cancer when standardised surgery, radiotherapy, and pathology are used, and to investigate whether the local recurrence rate after TME permits the omission of adjuvant preoperative radiotherapy. In this paper we describe the rationale and design of the trial and the baseline characteristics and short term morbidity of the first 500 randomised Dutch patients, to judge the feasibility of the trial.

PATIENTS & METHODS (DESIGN OF THE TRIAL)

A phase III trial "total mesorectal excision with or without preoperative radiotherapy in the treatment of primary rectal cancer" started in January 1996 under the auspices of the Dutch ColoRectal Cancer Group (DCRC-group). This trial evaluates the effect of preoperative radiotherapy in combination with standardised TME, focussing on recurrence rates, survival, operation-related factors, specific histopathological characteristics of tumours, short and long term morbidity, and quality of life.

The TME trial is a two-arm prospective randomised trial. Patients in arm A undergo standard TME alone. Patients in arm B are given preoperative radiotherapy (5 $\times$ 5 Gy) followed within 10 days of the start of radiotherapy by standard TME. Randomisation is done centrally at the Datacenter of Surgery at the Leiden University Medical Center, Leiden, The Netherlands. During randomisation patients are stratified by their hospital and type of resection (abdominoperineal resection or low anterior resection). The randomisation scheme is shown in Fig. 1. The inclusion and exclusion criteria of the trial are shown in Table I. Patients have been randomised from The Netherlands, England, Germany, Sweden, and Switzerland, but this paper will concentrate on the trial in The Netherlands.

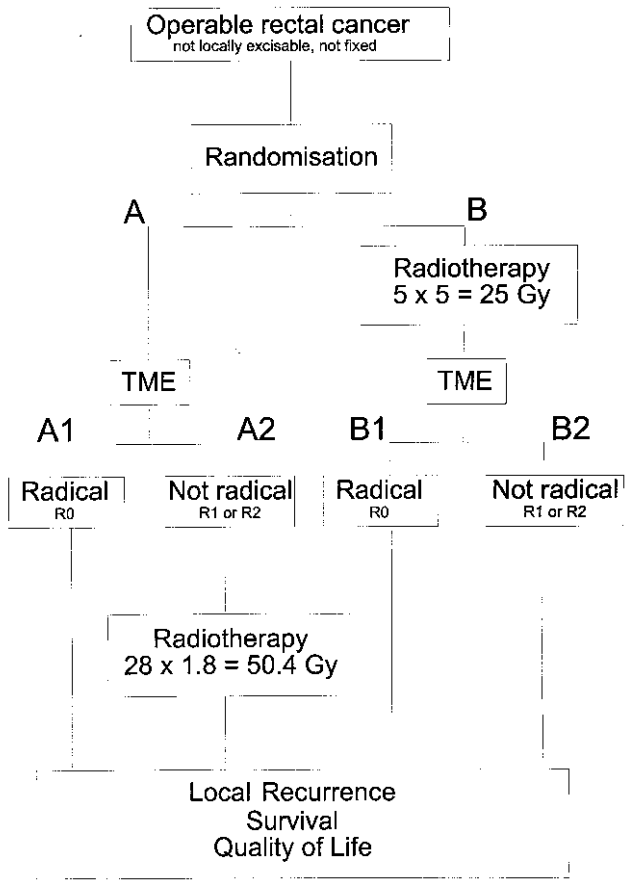

Fig. 1. Algorithm showing protocol of the trial.

Table I. *Inclusion and exclusion criteria*

Inclusion criteria
Patients with histologically confirmed adenocarcinoma of the rectum
Tumours located below the level of S1/S2 provided that the distal border of the tumour is within 15 cm of the anal verge (this being measured during withdrawal of a flexible scope)
The tumour must be clinically resectable. This is defined as any tumour which, on examination by the surgeon, is found to be mobile, indicating that margins are likely to be free of tumour (R0-resection, no evidence of residual tumour). Tumours fixed to the pelvic wall, the prostate or base of the urinary bladder are clinically assessed as T4 tumours and considered to be fixed and therefore not resectable, as an R0-resection cannot be achieved. The surgeon must record at pre-treatment examination whether the patient will require an abdominoperineal resection or low anterior resection
WHO performance status of 2 or less
Resection through a laparotomy incision
Informed consent according to the institutes' regulations
Age 18 years or more
Exclusion criteria
Any previous treatment for rectal cancer
Synchronous distant, clinically-documented metastases
Emergency operation
Inadequate potential for follow-up
Previous partial resections of left sided large bowel or rectum, or previous history of multiple or pelvic operations
Hereditary polyposis disease
Other malignancies except adequately treated basal cell carcinoma of the skin or in situ carcinoma of the cervix
Tumours which in the opinion of the surgeon can be excised locally
Previous chemotherapy, immunotherapy, or radiotherapy to the pelvis

TME is done according to strict and controllable quality demands. An extensive structure of workshops, symposia, and instruction videos has helped to accomplish this goal. In addition, a monitoring committee of specially trained consultant surgeons has been formed to optimise quality control. In each participating hospital the first five TMEs have to be supervised by a consultant surgeon. Professor Y. Moriya from the National Cancer Hospital, Tokyo, Japan, has been involved as visiting professor and operating surgeon in the pilot study for the trial (15). Professor R. J. Heald from North Hampshire Hospital, Basingstoke, England, and Professor W. E. Enker from Beth Israel Medical Center, New York, USA, have been involved as operating surgeons in different hospitals in The Netherlands and as instructors at several workshops.

Pathological examination is done according to the protocol of Quirke and Dixon (26). Special training courses have been given to pathologists. A pathology panel has been formed to guarantee quality control. Fresh frozen and paraffin material are collected from each randomised patient in a standard way for molecular biological research purposes. The residual tumour classification used is defined as follows: R0, no residual tumour; R1, microscopic residual tumour (tumour infiltration less than 1 mm from the resection margins or tumour spill during operation or positive cytology showing malignant cells); and R2, macroscopic residual tumour (residual distant metastasis or residual locoregional tumour).

The clinical target volume of the preoperative radiotherapy consists of the primary tumour and the mesentery with vascular supply containing the perirectal, the presacral, and the internal iliac nodes (up to the S1/S2 junction). Blocks in the lateral portals are used to cover the lordotic area behind the sacrum dorsally and if appropriate the ventral part of the vagina and part of the prostate ventrally. The dose is specified according to the ICRU 50 report and is 5×5 Gy. Patients are treated with megavoltage equipment and a multiple field technique is used. In patients having TME alone, postoperative irradiation is used when pathological examination shows infiltration of tumour less than 1 mm from the resection margins or when tumour has been spilt.

Quality of life assessments take place only for the Dutch patients before treatment and at 3, 6, 12, 18, and 24 months postoperatively by means of questionnaires. Both cost and effect analysis will be combined into a cost-utility analysis at the end of the trial, in which several regimens for rectal cancer surgery will be evaluated, with and without preoperative radiotherapy.

Measurement of the sample size of the trial is based on expected local recurrence rates in the two treatment arms. Assuming a local recurrence rate of 10% in arm A (R0 (no evidence of residual disease) resections without preoperative radiotherapy) and an additional reduction in local recurrence rate to 5% in arm B (R0 resections with 5×5 Gy preoperative radiotherapy), 1026 patients must be evaluated to detect this difference (significance level 0.05; power 0.90). An estimated rate of ineligible patients and patients with

Table II. *Intake into the trial per quarter*

	Number of patients	
Quarter	The Netherlands	Other countries
1st/1996	28	0
2nd	74	0
3rd	81	0
4th	91	5
1st/1997	117	6
2nd	120	18
3rd	123	20
4th	112	16
1st/1998	125	29

non-radical resections (R1 and R2) of 10% is expected in both arms, so 1140 patients have to be randomised.

In our feasibility analysis we used univariate analysis with the chi-square test to look for differences in morbidity and mortality between the randomisation groups.

RESULTS (FEASIBILITY ANALYSIS)

From January 1996 until April 1998, 871 patients were randomised in 80 hospitals in The Netherlands. A further 89 patients in nine Swedish hospitals, three patients in one German hospital, one Swiss patient and one English patient were randomised. The number of randomisations has increased almost every quarter. Table II shows the intake in each quarter up to April 1998.

We have evaluated the first 500 Dutch patients randomised. These patients were operated on in 67 hospitals. Eighteen radiotherapy institutes and 42 pathology departments were involved in the treatment. Table III shows the baseline characteristics of these patients both in total and by randomisation group. Twenty-eight patients (6%) were ineligible for the reasons given.

Table IV shows the radiotherapy variables of the eligible patients randomised for radiotherapy ($n = 222$). As the trial is ongoing, not all case report forms have been received, which automatically results in missing data in the tables. The median interval between radiotherapy and surgery was four days (range 1–55). Ninety-six percent of the eligible patients randomised

Table IV. *Radiotherapy variables of the eligible patients randomised to radiotherapy (*n = *222)*

Interval between radiotherapy and operation (days):	Median	4
	Range	1–55
	Not known	28
Compliance:	100%	180 (96)
	<100%	8 (4)
	Not known	34
Toxicity:	Acute skin/lower gastrointestinal or genitourinary toxicity	31 (16)
	Missing values	34
	Other toxicity	30 (19)
	Missing values	67
	Neurotoxicity	16 (10)
	Missing values	67

Data are expressed as number (%) of patients unless otherwise stated.

Table III. *Baseline characteristics of the first 500 randomised Dutch patients to radiotherapy plus total mesorectal excision (TME) or excision alone*

		Total	Radiotherapy + TME	TME alone
Randomised:		500 (100)	235 (47)	265 (53)
Eligible:		472 (94)	222 (94)	250 (94)
Ineligible*:		28 (6)	13 (6)	15 (6)
	Distant metastases	10	4	6
	Clinically non-resectable tumour	4		4
	No adenocarcinoma	3	2	1
	Hereditary polyposis disease	1		1
	Other previous malignancies	4	2	2
	Radiotherapy not possible	1	1	
	Previous treatment	2	1	1
	No informed consent	4	3	1
Sex:	Male	316 (63)	154 (65)	162 (61)
	Female	184 (37)	81 (35)	103 (39)
Age (years):	Mean	64	64	63
	Range	23–89	27–88	23–89

* One patient was ineligible by virtue of having distant metastasis and a clinically non-resectable tumour.
Data are expressed as number (%) of patients unless otherwise stated.

Table V. *Surgical variables of the eligible patients who had total mesorectal excision (TME)**

		Total ($n = 462$)	Radiotherapy + TME ($n = 219$)	TME alone ($n = 243$)
Attendance of consultant surgeon:		245 (58)	115 (59)	130 (58)
	Not known	42	24	18
Type of operation:	Low anterior resection	279 (64)	128 (63)	151 (65)
	Abdominoperineal resection	132 (30)	62 (30)	70 (30)
	Hartmann operation	24 (6)	14 (7)	10 (5)
	Not known	27	16	11
Intraoperative complications:		80 (20)	41 (21)	39 (18)
	Not known	54	26	28
Type of anastomosis in low anterior resection group:	Side-to-end	149 (56)	69 (56)	80 (56)
	End-to-end	26 (10)	12 (10)	14 (10)
	Pouch	90 (34)	41 (34)	49 (34)
	Not known	14	5	9
Type of stoma in low anterior resection group:	None	129 (48)	56 (44)	73 (50)
	Diverting	142 (52)	70 (56)	72 (50)
	Not known	8	2	6
Duration of operation (min):	Median	185	190	180
	Range	70–390	80–390	70–390
	Not known	52	29	23
Blood loss (ml):	Median**	1000	1200	800
	Range	50–5700	100–5700	50–5500
	Not known	54	32	22
Postoperative complications:	Overall	189 (46)	95 (51)	94 (43)
	Not known	54	32	22
	General	71 (17)	38 (20)	33 (15)
	Not known	52	29	23
	Infective***	128 (31)	69 (36)	59 (27)
	Not known	48	26	22
	Surgical	124 (30)	62 (32)	62 (28)
	Not known	48	26	22
No of leaks in low anterior resection group:		37 (14)	18 (15)	19 (13)
	Not known	12	8	4
Duration of postoperative stay (days):	Median	15.0	15.0	15.0
	Range	4–120	4–120	7–83
	Not known	38	20	18
Reoperations:		68 (16)	36 (19)	32 (14)
	Not known	48	32	16

* Ten of the 472 eligible patients did not have a resection; ** $p < 0.001$; *** $p = 0.04$.
Data are expressed as number (%) of patients unless otherwise stated.

for radiotherapy received the 5×5 Gy scheme according to the protocol. Adverse acute radiotherapeutic effects were acute skin, lower gastrointestinal, and genitourinary toxicity. These were reported in 16% of the irradiated patients in varying degrees. Other symptoms of acute toxicity varied from tiredness, tenesmus, nausea, loss of appetite, emesis, abdominal pain, and acute neurogenic pain of the lower lumbar region with or without radiation to the legs (neurotoxicity), and were reported in 19% of the cases in varying degrees. Neurotoxicity was reported in 10% of the irradiated patients in varying degrees.

Table V shows the surgical variables of the eligible patients ($n = 462$) who underwent TME. Ten patients did not have a resection because they had tumours that were found to be fixed during operation. Fifty-eight percent of the operations were attended by consultant surgeons. In non-reaching hospitals, this percentage was 50% (data not shown). For patients in the low anterior resection group with tumours which had a distal margin within 6 cm of the anal verge, the percentages of side-to-end, end-to-end anastomosis and pouch were 52%, 2%, and 46% (data not shown). In this group, 68% had a diverting stoma (data not

Table VI. *Histopathological variables of the eligible patients*

		Total ($n = 472$)	Radiotherapy + TME ($n = 222$)	TME alone ($n = 250$)
Residual tumour:	R0	328 (79)	151 (79)	177 (78)
	R1	48 (11)	24 (13)	24 (11)
	R2	41 (10)	16 (8)	25 (11)
	Not known	55	31	24
Involved circumferential margin:		54 (13)	26 (13)	28 (12)
	Not known	41	23	18
Lymph nodes examined:	Median*	8.0	7.0	9.0
	Range	0–52	0–47	1–52
	Not known	42	24	18

* $p < 0.001$.

shown). In low anterior resection patients there was no difference in leak rate between the randomisation groups. In total, there were 15 hospital deaths (3%, data not shown). Until now no significant difference has been seen between the two treatment arms with regard to the rate of hospital death.

Table VI shows the histopathological variables of the eligible patients randomised ($n = 472$). No residual tumour was found in 79% of the patients, 11% had microscopic residual tumour and 10% macroscopic residual tumour.

An interim analysis was made in September 1997, when the percentage of ineligible patients and patients with inadequate resections was found to be higher than expected; roughly 25% instead of the assumed 10%. As a consequence we will have to randomise (100/75) $\times 1026$ patients, nearly 1400 patients, to detect a difference of 5% in local recurrence rate between arms A and B (patients with R0 resections).

DISCUSSION

More than two years after the start of the TME trial, we can conclude that accrual has gone well, and it is obvious that the trial is feasible. Short term preoperative radiotherapy is safe even when combined with TME. We will discuss some important aspects of our feasibility analysis.

The great enthusiasm and interest for the TME trial can be explained by the need to evaluate the effect of short term preoperative radiotherapy together with "optimised" surgery. Large, prospective, Swedish trials of preoperative compared with postoperative radiotherapy have shown that preoperative radiotherapy is superior, both as regards local control and survival (23, 31). One explanation for the success of short term preoperative radiotherapy is that a high dose is given within a short time followed immediately by surgery. Another explanation is better compliance with preoperative radiotherapy than with postoperative radiotherapy.

Before starting the trial, we were afraid that morbidity and mortality would increase when we used preoperative radiotherapy with high dose fractions in combination with extensive surgery. However, the Swedish experience showed us that treatment volume and technique were critical with respect to morbidity and mortality. The volume and radiotherapy technique were therefore carefully described for this protocol with the help of Professor B Glimelius from Akademiska Sjukhuset, Uppsala, Sweden. We found significant differences between the randomisation groups only with regard to intraoperative blood loss (more in the radiotherapy + TME group) and the infective complication rate (also higher in the radiotherapy + TME group). The first finding is readily explicable as radiation causes more hyperaemia and increased vascularity. The second finding is also comprehensible by the adverse effects of radiation on wound healing and on local infection. We conclude from these findings that the preoperative radiotherapy scheme has adverse effects at the time of surgery. However, the additional morbidity may be acceptable if the ultimate rates of local recurrence or survival are improved.

Acute toxicity from the radiotherapy was reported in 16% (skin/lower gastrointestinal/genitourinary toxicity) and 19% (other toxicity) of the irradiated patients in varying degrees. One of the most severe acute side effects reported was acute neurogenic pain in the lower lumbar region with or without radiation to the legs, and was observed in 10% of the irradiated patients in varying degrees. Although radiobiological and radiotherapeutic data have suggested that doses higher than 25 Gy are needed to cause damage to the peripheral nerves, this type of acute neuralgia is observed in a few cases and can disable patients for a long time. According to the Swedish experience we therefore lower the upper border of the target volume, when a

patient develops this type of neuralgia, and try to complete the preoperative radiotherapy.

The cooperation between and within the participating disciplines is going well. With regard to the surgical part, this can be concluded from the large number (58%) of operations attended by specially trained consultant surgeons. Even when we evaluated only the non-teaching hospitals, the percentage was 50%. Obviously, this will come down because surgeons become experienced with the TME-technique after the first five operations that have to be attended by a consultant surgeon.

The TME trial will hopefully result in improved local control, survival, and morbidity. Another aim of improved outcome of the patients is to lower the number of abdominoperineal resections; until now only 30% of patients had one. This percentage is lower than that reported in other studies (3, 25). However, when doing a TME, operating time is increased to a mean of 3–4 hours (in our analysis the median operation time was 185 minutes) with the possibility of extra morbidity. The observed overall postoperative complication rate of 47% is considerable, but does not differ from other reports. Complication rates of 50% have been reported after conventional surgery (25). Several studies have reported overall anastomotic leak rates between 0 and 17.4% (3, 19, 25, 28). The leak rate of 14% in our trial is within this range. The hospital death rate of 3% is also within the range of other studies (3, 25, 28).

The use of a temporary colostomy is advocated if the distal margin of the tumour is located within 6 cm from the anal verge, because of the reported increased leak rate in these low tumours. The leak rate is also significantly reduced after side-to-end anastomosis (34) or pouch reconstruction (7). End-to-end anastomoses are therefore discouraged. In the group that had low anterior resections 52% had diverting stomas. This percentage was 68% for patients with tumours of which the distal margin was within 6 cm of the anal verge. In the low anterior resection group 56% and 34% of cases had side-to-end anastomoses and a pouch. These percentages were 52% and 46% respectively for patients with tumours with distal margins within 6 cm of the anal verge. These results show that the recommendations to keep the leak rate as low as possible are followed.

In the TME trial pathological examinination of the resected specimen follows the protocol of Quirke et al. This method gives a good examination of lateral margins and can predict the development of local recurrences (26, 27). The positive predictive values of involvement of the circumferential margins (<1mm) for local recurrence found in studies done by Quirke et al. and Adam et al. were 85% (27) and 53% (2), respectively. Involvement of the circumferential margin by tumour was seen in 27% (27) and 36% (2) of cases, respectively. In our study this percentage was 13% which is lower than reported in the studies by Quirke et al. and Adam et al. There was no difference in the number showing involvement of the circumferential margins between the randomisation groups. However, we did find a significantly lower median number of examined lymph nodes in the irradiated group. Some studies have shown that both normal and pathological lymph tissue can be reduced by irradiation (12, 18, 29). Further investigation will be done to examine the influence of short term preoperative radiotherapy on lymph tissue.

The TME trial is to our knowledge the first in the world in which the effect of short term preoperative radiotherapy combined with TME is evaluated. Standardisation of surgery, radiotherapy, and pathology has been achieved. The trial is obviously feasible. Up to now many patients have been randomised from a large number of hospitals in The Netherlands and from Sweden, Switzerland, Germany, and England. The cooperation between surgeons is going well which can be concluded from the large percentage of operations attended by consultant surgeons. The number of abdominoperineal resections in our trial is lower than reported in other studies, as is the percentage of involved lateral margins. With respect to the acute adverse effects of radiotherapy, we conclude that the degree of acute toxicity is acceptable. Apart from more peroperative blood loss and a higher infective complication rate in the irradiated group, we found no significant differences between the randomisation groups in postoperative complications and mortality. The design of the TME trial will hopefully result in a large reduction of the number of local recurrences. Such an ambitious goal cannot be reached without the enthusiasm of many. It is therefore encouraging that the trial is already guaranteed by the devotion of many colleagues.

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ADDENDUM

In the time between acceptation and publication of this paper the accrual has increased to 1212 patients from Dutch hospitals and 195 patients from foreign hospitals (up to January 1st 1999). The expectation is that the trial will close in June 1999. After that further reporting will take place. No differences have been found between our last feasibility analysis and the analysis described in this paper.

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RÉSUMÉ

But: Etudier les récidives locales après prise en charge standardisée tant du point de vue de la technique chirurgicale que de la radiothérapie et de l'examen histologique des cancers primitifs du rectum, et savoir si le taux de récidive locale après exérèse totale du mésorectum permet de surseoir à la radiothérapie courte préopératoire.
Type d'étude: Prospective, randomisée.
Provenance: Des hôpitaux hollandais ($n = 80$), anglais ($n = 1$), allemand ($n = 1$), suédois ($n = 9$), et suisse ($n = 1$).
Patients: Les 500 premiers patients hollandais qui ont été randomisés.
Principaux critères de jugement: Les récidives locales, la survie, les facteurs liés à l'intervention chirurgicale, les caractéristiques histologiques spécifiques de la tumeur, la morbidité à court et long terme et les études de qualité de vie.
Résultats: Entre Janvier 1996 et Avril 1998, 881 patients hollandais et 94 patients originaires d'autres pays ont été randomisés. Notre étude de faisabilité a montré qu'il y avait une bonne coopération entre les différentes disciplines et au sein même des différentes disciplines. En ce qui concerne la chirurgie, cela était confirmé par le nombre important d'interventions réalisées par des chirurgiens consultants (58%). Le nombre d'amputation abdominopérinéale est apparu bas (30%), de même que le pourcentage de limite latérale d'exérèse envahie (13%). Le pourcentage d'effets secondaires indésirables de la radiothérapie était acceptable. Mis à part des pertes sanguines peropératoires plus importantes et un taux de complication infectieuse plus élevé dans le groups des patients irradiés, il n'y avait pas de différence significative entre les groupes en ce qui concerne la morbidité et la mortalité.
Conclusions: Notre étude marche bien et a une bonne faisabilité; la radiothérapie courte préopératoire est sans danger même combinée à une exérèse totale du mésorectum.
Mots-clés: Etude prospective randomisée, cancer primitif du rectum, exérèse totale du mésorectum, radiothérapie préopératoire.

ZUSAMMENFASSUNG

Ziele: Dokumentation der Lokalrezidivrate primärer Rektumkarzinome unter Verwendung standardisierter Techniken für die Resektion, Radiotherapie und Pathologie, sowie Untersuchungen zur Frage, ob die Lokalrezidivrate nach totaler-mesorektaler-Exzision (TME) den Verzicht auf die adjuvante, kurzfristige präoperative Radiotherapie erlaubt.
Studienanordnung: Prospektiv randomisierte Studie.
Studienort: Holländische ($n = 80$), englische ($n = 1$), deutsche ($n = 1$), schwedische ($n = 9$) und schweizer ($n = 1$) Krankenhäuser.
Patienten: Die ersten 500 holländischen Patienten mit einem primären Rektumkarzinom, die innerhalb dieser Studie randomisiert wurden.
Endpunkte: Lokalrezidiv, Überleben, operationsbezogene Faktoren, spezifische pathologische Tumorcharakteristika, Kurz- und Langzeitmorbidität sowie Aspekte der Lebensqualität.
Ergebnisse: Zwischen Januar 1996 und April 1998 wurden 881 Patienten und 94 Patienten aus den anderen Krankenhäusern randomisiert. Die Durchführbarkeitsanalyse zeigte, daß die Kooperation zwischen und innerhalb der verschiedenen, teilnehmenden Disziplinen gut war. Im Hinblick auf die chirurgische Behandlung wurde diese durch die hohe Zahl der Operationen, bei denen ein leitender Chirurg anwesend war, unterstrichen (58%). Die Anzahl der abdominoperinealen Resektionen erschien niedrig (30%), wie auch der prozentuale Anteil infiltrierter lateraler Resektionsgrenzen (13%). Die Rate unerwünschter Nebeneffekte der Radiotherapie war akzeptierbar. So wurde in der Gruppe der vorbestrahlten Patienten im Vergleich zu den anderen randomisierten Gruppen, abgesehen von einem höheren intraoperativen Blutverlust sowie einer höheren Infektionsrate keine signifikanten Differenzen im Hinblick auf Morbidität und Mortalität gesehen.
Schlußfolgerungen: Die Initialphase dieser Studie verläuft günstig und belegt ihre Durchführbarkeit; die präoperative Kurzzeitstrahlenbehandlung ist auch in Kombination mit der TME eine sichere Behandlungsnahme.
Schlüsselwörter: Prospektiv randomisierte Studie, primäres Rektumkarzinom, TME, präoperative Radiotherapie.

РЕЗГОМЕ́

Цель: Документировать локальные рецидивы первичного ректального рака после стандартной хирургии, радиотерапии и патологического исследования, и изучить взаимосвязь локальных рецидивов после трансмезоректальной эксцизии (ТМЭ) с отсутствием предоперативной адъювантной радиотерапии.
Характер исследования: Проспективное рандомизированное исследование.
Клиника: 80 датских, 1 английская, 1 немецкая, 9 шведских и 1 швейцарская клиника.
Пациенты: Пациенты с первичным раком прямой кишки, которые были рандомизированы.
Задачи исследования: Изучение локальных рецидивов, выживаемости, аспектов, связанных с операцией, специфических патологоанатомических характеристик опухоли, а также ранних и поздних послеоперационных осложнений и качества жизни.
Результаты: За период времени с января 1996 года по апрель 1998 года 881 датских и 94 зарубежных пациентов были рандомизированы. Проведенный анализ показал, что кооперация между участниками исследования была хорошей. Согласно протоколу было подтверждено, что большая часть операций проводилась старшими хирургами (58%). Количество абдомино-перинеальных резекций было меньше 30%; процент наличия опухолевых клеток в крае резекции составил 13%. Процент негативных эффектов радиотерапии был приемлемым. Кроме большей интраоперативной потери крови и большего процента инфекционных осложнений в группе лечевой терапии, не было отмечено статистически достоверной разницы по проценту летальности и

послеоперационных осложнений между рандомизированными группами.
Выводы: Точность проведения данного исследования была хорошей. Кратковременная предоперативная радиотерапия в сочетании с ТМЭ является безопасным методом.
Ключевые слова: Проспективное рандомизированное исследование; первичный рак прямой кишки, ТМЭ-хирургия; предоперативная радиотерапия.

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