Population-based randomized multi-center study on the value of different radiation treatment models for primary operable rectal cancer

Background

The Regional Care Group for rectal, later colorectal, cancer in the Stockholm-Gotland region has existed since 1980. Since then, it has initiated three population-based randomized studies, of which one has been completed, one will be completed within one to two years, and the third is underway. The first study examined the value of preoperative radiation therapy with 5 x 5 Gy for one week before surgery. In the study, large-volume radiation therapy was administered as introduced by Kliegerman and the treatment was performed against the near field and far field with cobalt or with a linear accelerator. After at least five years’ follow-up, the study showed a 50% reduction of local recurrence in the group treated with radiation, but also significantly increased postoperative mortality, in particular in patients over 80 years of age, and both increased early and late postoperative morbidity. In late morbidity, an increased number of pelvic fractures was also seen, an increased number of fistulas and increased frequency of thrombo-embolic diseases.

In 1987, the study protocol was changed so that an upper age limit of 80 was introduced, and radiation therapy was changed so that this was performed using a four-field technique instead of a lower volume using only a linear accelerator (Study II). The five-year evaluation will be done in 1998-99, but a primary evaluation done in 1994 showed that the altered technique and the new age limit achieved an extended survival rate with respect to rectal cancer specifically, at least 50% reduction of local recurrence, and reduction of distant metastases in patients receiving radiation therapy compared with those who received surgery alone. There was no significant postoperative mortality. Late morbidity was increased in patients receiving radiation therapy, but less pronounced than in the first study.

In large areas of the rest of Sweden, a corresponding multi-center study was conducted at the same time as the second study. This multi-center study used a three-field or four-field technique, but otherwise had the same inclusion criteria and treatment principles. An evaluation of this study, which included 1,167 patients (of which 315 were also part of Stockholm Study II), confirmed the increased survival rate after at least five years’ follow-up as well as a significant increased “overall” survival. A 60% reduction of local recurrence occurred. No significant different in postoperative mortality was proven. No analysis of late morbidity was performed in this study.

Thus in Stockholm, over 1,400 patients with clinical primary operable rectal cancer have been included in population-based studies regarding the effect of preoperative radiation therapy. A preliminary evaluation of tumor sizes in patients treated with or without radiation therapy shows significantly smaller tumor sizes in the group treated with radiation therapy. Further, we have found that patients who for different reasons have had a relatively long interval between completed radiation therapy and surgery sometimes present with very small tumor residual at the time of surgery. Corresponding good effects of radiation therapy have also been reported by other studies with more conventional radiation therapy over a longer period of time and with a three- to six-week break between completed radiation therapy and surgery.
The development of the surgical technique during the past decades has been rapid. Stapling instruments have come into use, which provides the opportunity for long anastomoses and sphincter-sparing surgery to a larger extent than previously. Total mesorectum extirpation (TME), which was introduced by Healt and his colleagues during the 1980s, has come into general use in the Stockholm region after active regional training efforts. TME has also shown the ability to reduce local recurrence frequency without adjuvant radiation therapy at individual centers for rectal cancer surgery. Whether this applies from a population perspective – when many hospitals and surgeons are involved – is however not yet proven.

It has been recently asserted (Heald et al.) that rectal amputation in and of itself could be an operation that involves an increased number of local recurrences because of the large wound area that is vulnerable to possible implantation metastases. Therefore, it has been decided that one attempt to attain lower anterior resections to the fullest extent possible and, where needed, to combine these with an assistive ostomy for a period of time or, if necessary, permanently. Preoperative radiation therapy with postponed operation could eventually result in more patients with low-seated tumors becoming eligible for sphincter-sparing surgery as the size of the tumor decreases.

**Purpose**

Comparing treatment with “conventional” fractionation (25 x 2 Gy) of adjuvant preoperative radiation therapy with a corresponding biological radiation dose given in few, larger fractions (5 x 5 Gy) and studying possible significance of the length of the interval between completed radiation therapy and surgery.

**Problem**

Is preoperative radiation therapy administered for 5-6 weeks and with “conventional” fractionation (2 Gy x 25), followed by surgery after 4-8 weeks, preferable to treatment with 5 x 5 Gy during one week + surgery within one or after 4-8 weeks? Are there clinically significant differences in local recurrence frequency, survival rate, postoperative morbidity and mortality or late morbidity? Is the need for ostomy reduced if surgery is delayed?

**Inclusion criteria**

- Clinically primary operable, prognosis-verified adenocarcinoma of the rectum. No signs of distant metastases.
- Surgery is planned as a transabdominal procedure.
- Patient without sign of ischemic cardiac disease or symptomatic arteriosclerosis.
- No previous radiation therapy of the abdomen or pelvic area.
Statistical considerations

Endpoints

The primary endpoint of the study is the time until local recurrence. Secondary endpoints are: survival rate, postoperative mortality (within 30 days), proportion of postoperative complications (see definition below), proportion of patients requiring reoperation, late morbidity (see definition below), proportion of patients who can receive sphincter-sparing surgery with or without assistive ostomy.

Stratification

Stratification will only be done for participating clinics / hospitals.

Randomization

Patients who fulfill the inclusion criteria and who have submitted their consent to participate in the study will be randomized into one of the following three treatment alternatives:

1. Preoperative radiation therapy 25 x 2 Gy with surgery after 4-8 weeks.
2. Preoperative radiation therapy 5 x 5 Gy with surgery within one week.
3. Preoperative radiation therapy 5 x 5 Gy with surgery after 4-8 weeks.

Patients will be assigned a treatment alternative according to the principle of blockwise randomization, in which after each consecutively collected patient group, balance is confirmed with respect to the number of patients in each respective treatment arm. The patients will be randomized according to the relationship 1 : 1 : 1, that is, equal numbers in each treatment arm.

Before contact is made with the Oncology Center for randomization, the reporting doctor fills out a randomization form with information about the study’s inclusion and exclusion criteria. After the patient has been randomized, a faxed verification of assigned treatment will be sent to the reporting doctor / clinic.

Randomization of patients is performed by the Oncology Center, Monday – Friday 8:00 a.m. – 4:00 p.m. at phone number +46 8-517 72981.

Dimensioning

With preoperative radiation therapy 5 x 5 Gy, after five years the incidence of local recurrence is expected to reach 15% and survival 60%. This is accompanied by a constant annual recurrence risk of 3.3% and a constant annual risk of death at 10%. The proportion of postoperative complications is estimated at 15% and the proportion of patients with sphincter-sparing surgery at 50%.

The primary endpoint of the study: the time before local recurrence creates the basis for calculations of patient number, expected number of events and strength.

The treatments are considered of equal value (equivalent) with respect to the incidence of local recurrence if a worsening in condition corresponding to a relative hazard larger than 1.7 can be excluded. After five years, a relative hazard of 1.7 means an increase of incidence of local recurrence from 15% to 24%, that is, an absolute worsening of 9.1%.
The following treatment comparisons are planned:

A. Preoperative radiation therapy administered over a longer period of time and with conventional fractionation 25 x 2 Gy with surgery after 4-8 weeks is compared with preoperative radiation therapy 5 x 5 Gy with surgery within one week or with surgery after 4-8 weeks.

B. A longer interval (4-8 weeks) between radiation therapy, regardless of fractionation, and surgery is compared with a shorter interval (< one week).

C. A longer interval (4-8 weeks) between radiation therapy and surgery is compared to a shorter interval (≤ one week) in patients who received radiation therapy with 5 x 5 Gy.

In both comparisons, the equivalence between the treatment alternatives will be concluded if the upper limit in a double-sided 90% confidence interval for relative hazard does not exceed 1.7 in the analysis of local recurrence. This is the same as performing a single-sided test at a 5% significance level.

Against the background of previous studies, it is considered realistic to recruit 100-120 patients from the Stockholm – Gotland region annually. A study including a total of 840 patients (that is, recruitment of 120 patients per year for seven years) and with a minimum follow-up period of two years is expected to have generated a total of 100 local recurrences (taking into consideration 10% annual mortality) and 350 deaths at the point of the statistical analysis. With 840 patients and with the conditions given above, the study has a strength of 80% of demonstrating similarity with respect to the incidence of local recurrence in comparisons A and B. In comparison C, the study has a strength of 70%. Regarding survival rates, the study has a strength of 75% to demonstrate similarity, defined as excluding a relative hazard of 1.3, in comparisons A and B, and 64% in comparison C. (A relative hazard of 1.3 means an absolute worsening in five-year survival of 8.5%, that is from 60% to 51%).

Statistical methods

Calculation and graphic presentation of survival and cumulative incidences will be performed according to the Kaplan-Meier method. The Cox regression model will be used for proving the hypothesis and in assessment of treatment effects. Models containing terms for baseline age, gender and Dukes classification will be adapted to adjust for potential confounding. This model, determined in advance, will also contain interaction terms between treatment and named factors with the purpose of studying if the treatment effect is constant for different factor levels.

Treatment effects are expressed as relative hazards with the associated 90% confidence interval. All analyses will be performed according to the principle of “intention to treat”, which means that all patients are included in the statistical analysis for the group into which they have been randomized.

Definitions for the statistical analysis

Time to event: (Local recurrence or death) is calculated from the randomization date to the date of recurrence or death. Patients who do not have an event will be censored at the latest follow-up date.

Survival: Time until death regardless of reason for death.
Incidence of local recurrence: Local recurrence or death, whichever occurs first. A patient who dies without prior local recurrence is censored from the analyses upon the date of death.

Postoperative mortality: Death within 30 days after the operation.

Postoperative complication: Cardiovascular, infectious, surgical (wound infection, intra-abdominal infection, bleeding, anastomotic insufficiency, wound rupture, urological complication).

Reoperation: Operation as a consequence of a postoperative complication.

Late morbidity: One or more symptom-producing illnesses, fractures of the pelvic region, symptomatic ileus, fistulas.

Randomization

Patients who fulfill the inclusion criteria and who have submitted their consent to be included in the study are randomized into one of the following alternatives:

1. Preoperative radiation therapy with 5 x 5 Gy with surgery within one week.
2. Preoperative radiation therapy with 5 x 5 Gy and surgery after 4-8 weeks.
3. 25 x 2.0 Gy and surgery after 4-8 weeks.

Radiation therapy will be administered with a linear accelerator against the tumor including the entire mesorectum according to individual radiation planning with the help of CT or MR.

Preoperative examination

- Clinical examination and rectoscopy with description of size of tumor, type of growth (circular, ulcerated, polyposis etc.) and distance in cm between the outer edge of the anal sphincter and the tumor’s lower border.
- Lung x-ray and ultrasound (alternatively CT or MR) of the liver.
- Colonoscopy or x-ray of the colon (in order to rule out the existence of further tumors).
- Blood count

The patient will be examined by MR or CT of the pelvis before commencement of radiation therapy. The patients who are randomized to “delayed” surgery should in addition, if possible, be examined within a week before surgery. The purpose of the first examination is to evaluate the size and position of the tumor so that the patient can receive an optimal, individually planned course of radiation therapy. The other examination will make it possible to study the effect of radiation therapy on the size of the tumor and its possible significance for the possibility of performing sphincter-sparing surgery.
Preoperative radiation therapy

shall follow the recommendations below. In the event of deviations from the recommendations, the type and reason shall be documented on the study form.

Dosage planning: Individual dosage planning based on information from the CT or MR study.

Treatment position: supine.

Treatment technique: The three-field or four-field technique is recommended, but more advanced techniques may be used if desired. The two-field technique shall be avoided unless special reasons exist in an individual case.

Radiation quality: Photon radiation with energy of $>8$ MV.

Definition of volumes:

GTV (Gross Tumor Volume): includes macroscopic tumor.

CTV (Clinical Target Volume): includes GTV and margins for subclinical spread of tumor cells as well as for temporal variations in size and position of anatomical structures in the body. The perirectal, obturator and iliac lymph nodes stations up to the level of the promontory shall be included in the CTV. In the case of low-seated tumors, the perineum comprises the caudal border of the CTV; in other cases, the CTV’s caudal border should lie at least 4 m below the GTV’s most caudal border.

PTV (Planning Target Volume): Includes CTV as well as margin for uncertainty in the positioning of the patient and the technical performance of the radiation therapy apparatus.

Dosage specification: Dosage shall be specified in the interface of the central rays. If the treatment technique with two opposing fields is used despite what is specified in the section “Treatment techniques” above, the dosage specification point shall be chosen centrally in the CTV. The dose homogeneity within the PTV should be $\pm 5\%$ or better. In addition to this point dose, the average dose in the CTV shall also be indicated.

Fractionation pattern and final dose: Randomization occurs between two alternatives. Patients belonging to the control arm are treated with 5.0 Gy/fraction on five treatment days during one week (Monday – Friday, Tuesday – Monday etc.) up to the final dose of 25 Gy. Patients belonging to the study arm will receive treatment with 2.0 Gy/fraction and five fractions/week up to the final dose of 50 Gy. If for any reason there is an interruption in the radiation therapy period, no adjustment of fraction of dose, daily dose or total dose shall be done in the control arm. In the study arm, however, for the purpose of keeping the total radiation therapy period constant in relation to the original schedule, two fractions can be administered in one day, as long as the time between the fractions is at least six hours and as long as there are no more than two extra fractions administered per week. The fraction or total dose shall, however, not be adjusted.

The beginning and ending dates of the radiation therapy shall be indicated on the study form as well as the reason for an extended treatment period in relation to “ideal time” (four respectively 32 24-hour days) if the extension exceeds five 24-hour days.
Surgery

shall be performed utilizing antibiotic prophylaxis and thrombosis prophylaxis.

shall be performed with low frontal resection with or without assistive ostomy when possible. Otherwise, amputation of the rectum or operation according to Hartmann shall be performed. The TME technique is the model to be emulated. If the surgeon for any reason does not perform TME (for example, a tumor located high where the surgeon decides to divide the mesorectum or when TME is not performed for technical reasons), this shall be reported. Anastomosis shall be performed all the way to the side or in the form of a “pouch”. The surgical report shall indicate whether the operation is considered to be locally radical or not, respectively curative or not.

Histopathology

Surgical specimens should be sent uncut to the appropriate pathology clinic so that the pathologist in charge can make a macroscopic evaluation of the resection borders including the lateral resection border. The uncut specimen shall first be rinsed intraluminally with salt and thereafter filled with 4% buffered formalin. The entire specimen shall be placed in a bucket in 4% buffered formalin and fixed for at least three days. Regarding “large section embedding” see the attachment. The pathologist in charge shall submit the completed Form 3 (Histopathology) to the Oncology Center in accordance with the regional care program in force for colorectal cancer in the Stockholm-Gotland region.

Follow-up

The patient will be followed up three, six and twelve months after surgery and annually thereafter. In the event of suspected local recurrence, MR preferably (possibly CT) shall be done of the pelvis before a decision is made as to course of action. Examinations otherwise shall be performed as needed in relation to symptoms and clinical findings. Suspected recurrences and/or metastases shall be verified cytologically / histologically when this is reasonable and possible. In the event of death, an autopsy should be pursued. Recording of medical history and possible examination to determine postoperative sphincter function or ostomy function as well as any “late” complications or morbidity shall be done upon each contact with the patient and be reported.

Parameters for study

1) Frequency of clinically curative respectively locally radical surgery 2) postoperative mortality 3) postoperative complications 4) late morbidity (fractures, fistulas, thromboembolisms etc.) 5) sphincter and/or ostomy function 6) frequency of local recurrence 7) distant metastases 8) five-year survival rate. Tumor size, percentage of patients who can receive sphincter-sparing surgery with respectively without supportive ostomy.

Patient information

All patients are informed verbally and in writing according to patient information approved by KI’s [Karolinska Institut] ethics committee.
Publication

The results shall be published under the name Stockholm Colorectal Cancer Study Group in accordance with the prevailing tradition to this point.

References


We hereby apply for review of a supplement to the study protocol “The value of different radiation treatment models in primary operable rectal cancer,” ID no. 98:240.

Project director: Björn Cedermark, professor, senior physician, Department of Surgery, Karolinska Hospital, 171 76 Stockholm

Employees: Regional care group for colorectal cancer in the Stockholm-Gotland region

The supplement to the study protocol including complementary patient information is attached.

Yours sincerely,

[Björn Cedermark
Professor, Senior Physician
Department of Surgery, Karolinska Hospital
Convener for the Regional Care Group for Colorectal Cancer in the Stockholm-Gotland Region]
Supplement to study protocol

Summary
Since the study was initiated in the fall of 1998, new information has been discovered which may have significance for the dimensioning and design of the study. This new information deals with the possibility of including patients in all three study arms and the expected risk for local recurrence and the side effects of radiation therapy. These conditions justify a supplement to the protocol which means a stratification between patients who are randomized to the study’s three current treatment arms according to the original protocol, respective patients who for different reasons can only be randomized to two of the study arms (radiation therapy 5 Gy x 5 with surgery within approximately one week respective 5 Gy x 5 with surgery after 4-8 weeks). The uncertainties that are inherent in the expected recurrence risk and the possibly increased possibilities of performing sphincter-sparing surgery if surgery is postponed justify an interim analysis of the study.

Randomization to two or three treatment arms?
The original protocol meant randomization to three treatment arms where the first arm means radiation therapy with “conventional” fractionation 2.00 Gy x 25 (alternative 1), and the other two arms the fractionation that to this point has been used in the Stockholm area, that is 5 Gy x 5 (alternatives 2 and 3). Since patient recruitment started in October 1998, it has become evident that certain patients could not be included in the study because the treatment alternative with “conventional” fractionation was not evaluated to be possible. Reasons for this include the patient’s desire for a short treatment period, practical problems at the radiation therapy departments because of operational interruption in the treatment apparatus, etc. For many of these patients, however, it would have been possible to be randomized between two treatment alternatives with a shorter radiation therapy period (alternatives 2 and 3). For this reason, it is justified that, for each patient that fulfills the study’s inclusion criteria, it be decided whether randomization shall be performed between the original three arms, or if randomization shall only be done between alternatives 2 and 3. In this way, patients who could not be included now at all in the study can at least contribute with information regarding the comparison between these two treatment arms.

Inclusion of a separate stratum with randomization between alternatives 2 and 3 does not change the need for the number of patients and events in the study in order to achieve an adequate statistical strength in the different treatment comparisons as indicated in the original protocol. On the other hand, it can be expected to turn out thus that the statistical strength desired is achieved earlier for comparisons between treatment alternatives 2 and 3 than for comparisons that include treatment alternative 1. This is however completely dependent upon the distribution of randomizations in the different strata, something that is difficult to judge in advance.

Risk of local recurrence
The dimensionalization of the present study has been based on a cumulative risk for local recurrence among patients receiving radiation therapy of 15%. Such a risk level is in agreement with results from randomized studies in the Stockholm area that recruited patients during the 1980s up to the beginning of the 1990s. Preliminary population-based data for rectal cancer patients during the middle of the 1990s speaks however in favor of the risk for local recurrence has been reduced, possibly as a result of the introduction of a new surgical technique (TME, Total Mesorectal Excision) at several hospitals in the region (Oncology Center 1999, unpublished data).
An analysis has been conducted for the purpose of describing the study’s statistical strength to exclude clinically significant differences between the treatment arms with respect to frequency of local recurrence under the assumption of a lower frequency of local recurrence than 15%, see Table 1. The table illustrates that with a similar but lowered frequency of local recurrence in the treatment arms, the lowest relative hazard increases (one of the treatment arms against the other two) that the study can exclude. On the other hand, this increased relative hazard corresponds to a lesser difference in cumulative frequency of local recurrence expressed in absolute numbers, that is even if the frequency of local recurrence in the treatment arms sinks to as low as for example 1%, the study can exclude a risk increase in one of the arms exceeding approx. 6.3%, which corresponds to a relative hazard of 7.3.

Table 1: Relative and absolute differences that the study can exclude under different assumptions about background incidence of local recurrence. Conditions: 840 patients, balanced randomization between the three treatment alternatives, alpha: 0.05 (single-sided test), 1-beta: 0.80, two-year follow-up, 10% annual mortality, comparisons made between two treatment arms against the third, that is 5 Gy x 5 against 2 Gy x 25, alternatively immediate surgery against “delayed surgery”.

<table>
<thead>
<tr>
<th>Cumulative incidence of local recurrence after 5 years, %</th>
<th>Annual risk of recurrence, %</th>
<th>Total number of recurrences (E)</th>
<th>Critical limits given E: Hazard rate/absolute difference at 5 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>3</td>
<td>96</td>
<td>1.7/10.5</td>
</tr>
<tr>
<td>12.5</td>
<td>2.5</td>
<td>81</td>
<td>1.8/10.0</td>
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<tr>
<td>10</td>
<td>2</td>
<td>66</td>
<td>1.9/9.0</td>
</tr>
<tr>
<td>7.5</td>
<td>1.5</td>
<td>50</td>
<td>2.1/8.3</td>
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<tr>
<td>5</td>
<td>1</td>
<td>34</td>
<td>2.5/7.5</td>
</tr>
<tr>
<td>2.5</td>
<td>0.5</td>
<td>17</td>
<td>3.6/6.5</td>
</tr>
<tr>
<td>1</td>
<td>0.2</td>
<td>7</td>
<td>7.3/6.3</td>
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</tbody>
</table>

Side effects
Long-term side effects comprise a secondary endpoint in the study. An important motivation for studying a treatment alternative with lower one-time fractions (that is 2 Gy x 25) is that such a fractionation, in theory, can be related to a lower frequency of late side effects and that previous studies have indicated an increase in certain defined side effects such as femural fractures and faulty sphincter functioning with the fractionation 5 Gy x 5 used thus far. A review of the radiation therapy techniques used routinely in the Stockholm region over the past years has however indicated that a reduced frequency in side effects should be able to be achieved simply through technical improvements meaning lower radiation doses to the surrounding organs at risk (C Svensson, B Glimelius, personal correspondence 1999). Such a reduction can be expected to reduce the study’s strength in proving clinically relevant differences between the different fractionation alternatives. At the present time, however, there are no clinical data regarding to what extent technical improvements can be expected to reduce the frequency of side effects and thus affect the study’s statistical strength in this respect.

“Down-staging”
“Down-staging” after radiation therapy followed by “delayed” surgery can potentially lead to more sphincter-sparing surgeries. The frequency of these also comprises a secondary endpoint. Statistical
considerations however show that clinically significant “down-staging” leading to an increased frequency of sphincter-sparing operations (for example from 60% to 75%) can be proven with adequate statistical strength with a smaller number of patients than what is needed in order to analyze the study’s primary endpoint, local recurrence (see Tables 2 and 3). That being said, this lower figure gives too low a strength to analyze whether a possibly increased frequency of sphincter-sparing operations is associated with an increased frequency of local recurrences. Such an analysis requires the originally planned number of patients, see Table 1.

Table 2: Necessary total number of patients for discovering an increase in the proportion of sphincter-sparing procedures from the current 60% (two-armed comparison, alpha=0.05, 1-beta=0.80)

<table>
<thead>
<tr>
<th>Increase from 60% to</th>
<th>Single-sided test</th>
<th>Double-sided test</th>
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<tbody>
<tr>
<td>65%</td>
<td>2,318</td>
<td>2,942</td>
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<tr>
<td>70%</td>
<td>562</td>
<td>712</td>
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<tr>
<td>75%</td>
<td>240</td>
<td>304</td>
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<tr>
<td>80%</td>
<td>128</td>
<td>164</td>
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Table 3: Study strength (1-beta) to discover a change in the stage distribution as a result of “down-staging” given the fact that a total of 300 patients were recruited at the time of analysis (two-armed comparison). Distribution of stage according to Dukes’ in the control arm can be assumed to be A 1/3, B 1/3, and C 1/3.

<table>
<thead>
<tr>
<th>An increase from 30% to</th>
<th>Single-sided test, %</th>
<th>Double-sided test, %</th>
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<tr>
<td>40</td>
<td>56</td>
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<td>50</td>
<td>97</td>
<td>94</td>
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**Quality of life**

Evaluating quality of life in the study is urgent since preoperative radiation therapy can cause side effects such as worsening of sphincter functioning. It is possible that the treatment arm with 2 Gy x 25 is better from this perspective than the treatment arms with 5 Gy x 5. A protocol for evaluation of symptoms, side effects and quality of life within the context of the present study is therefore in the process of being developed and will be presented to the ethics committee for evaluation. It can be anticipated that clinically significant results in terms of quality of life can be obtained with a lower number of patients than the 840 which are required for illuminating the effects on the study’s primary endpoint, local recurrence.

**Interim analysis**

Against the background of the conditions and considerations presented here, conducting an interim analysis of the study is justified after approximately 300 patients have been recruited to the two-armed comparison between alternatives 2 and 3. The interim analysis will consider the cumulative frequency of local recurrence. The comparison between the treatment arms in terms of this endpoint will not be done since the statistical strength to prove a clinically relevant difference would be insufficient, and since multiple significance testing would worsen the study’s final possibilities for generating dependable results. The purpose is simply to evaluate whether the frequency of local recurrence in the study is so low (possibly as a result of changed surgical/radiotherapeutical techniques) that the study’s dimensioning should be revised.

A comparison will also be made of the scope of “down-staging” and the frequency of sphincter-sparing surgery among patients who have been randomized between alternatives 2 and 3, that is 5 Gy x 5 followed by immediate surgery, alternatively 5 Gy x 5 followed by “delayed” surgery. If a statistically significant and clinically meaningful difference can be proven in these regards between the treatment arms, this can possibly justify a decision to cease recruitment into the treatment arm with immediate surgery. In such a possible decision, it will also be weighed in the study’s strength for proving differences in frequency of local recurrence between the different arms.

The interim analysis will also give information about the pace of recruitment in the two different patient strata, that is the three-armed comparison against the two-armed comparison, which is of significance for the study’s final dimensionization.

Attachment: Patient information for the two-armed comparison
RANDOMIZATION FORM

DIFFERENT RADIATION THERAPY MODELS FOR PRIMARY OPERABLE RECTAL CANCER

The questions below will be asked when you call for randomization of patients. You may fill in your own form before you call or fax to the Oncology Center, Stockholm, for randomization. Randomization can be done between 8:00 a.m. and 4:00 p.m. on weekdays. You may phone +46 8-517 72981 or fax +46 8-517 75444.

Remember to include your own fax number; the Oncology Center will fax a verification of randomization to you.

<table>
<thead>
<tr>
<th>PATIENT INFORMATION</th>
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<tbody>
<tr>
<td>Patient Social Security number</td>
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<tr>
<td>Patient name</td>
</tr>
<tr>
<td>Randomization date</td>
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<tr>
<td>Date of primary diagnosis of rectal cancer (for example patho-anatomical diagnosis date)</td>
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<table>
<thead>
<tr>
<th>STRATIFICATION</th>
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<tbody>
<tr>
<td>1. Which study will the patient be included in: □ the two-armed □ the three-armed</td>
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<tr>
<td>2. At which hospital will the patient have surgery:</td>
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<tr>
<th>INCLUSION CRITERIA</th>
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<tr>
<td>1. Does the patient have a clinically primary operable, patho-anatomical diagnosis verified, invasive adenocarcinoma in the rectum</td>
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<tr>
<td>2. The operation is planned with a transectional procedure (laparoscopic procedure OK)</td>
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<tr>
<td>3. Is the patient informed about the study and has s/he given his or her consent</td>
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<tr>
<th>EXCLUSION CRITERIA</th>
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<tr>
<td>4. Are there any signs of distant metastases</td>
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<tr>
<td>5. Does the patient have signs of ischemic heart disease, symptomatic arteriosclerosis or other symptoms that should rule out radiation therapy</td>
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<tr>
<td>6. Has previous radiation therapy been administered to the abdomen or the pelvic region</td>
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</tbody>
</table>

If all the boxes that have been checked are within the larger boxes, the conditions for randomization have been fulfilled and you may now contact the Oncology Center for randomization.
INFORMATION FROM THE ONCOLOGY CENTER REGARDING RANDOMIZATION

Randomization criteria checked by …………………………………………………………………………………………………………..

Name OC

<table>
<thead>
<tr>
<th>Treatment assigned:</th>
<th>TWO-ARMED</th>
<th>THREE-ARMED</th>
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</thead>
<tbody>
<tr>
<td>□</td>
<td>□</td>
<td>A. Preoperative radiation therapy with 5 x 5 Gy with surgery within one week</td>
</tr>
<tr>
<td>□</td>
<td>□</td>
<td>B. Preoperative radiation therapy with 5 x 5 Gy with surgery in 4-8 weeks</td>
</tr>
<tr>
<td>□</td>
<td>□</td>
<td>C. Preoperative radiation therapy with 25 x 2 Gy with surgery after 4-8 weeks</td>
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</tbody>
</table>


Information for you
for whom radiation therapy has been recommended before surgery for colon cancer

Colon cancer is a rather common occurrence in Sweden. Treatment consists of surgery in which the tumor is removed along with surrounding tissue with as good a margin as possible at the same time as an attempt is made to maintain significant tissues nearby to the largest extent possible (sphincter, nerves connected with sexual function and urination, etc.). In order to achieve this with the smallest possible risk for a return of the tumor in the surgical area, we combine the surgery with radiation therapy administered before the operation. This is to kill any cancer cells near the surgical margin, but also to try to reduce the size of the tumor.

Radiation therapy as it is used today is given for a week directly preceding the operation. This reduces the risk of recurrence, but it can also produce a number of side effects. We have thus seen that patients who have received radiation therapy in a higher extent get wound infections after the operation. In addition, we know that there is an increased risk for blood clot formation and bone breaks in the pelvic area later in life. These risks and the problems they cause are however small in comparison with the consequences of a return of tumors.

By giving radiation therapy in another way (more frequent and smaller doses over a longer period of time), there is in theory reason to believe that the side effects can be reduced at the same time as the reduced risk for recurrence is maintained or even improved further. It is also possible that the tumor size can be reduced if the time between radiation therapy and surgery is extended for 1-2 months. This in turn could possibly result in a greater chance of removing the tumor without risking damage to surrounding significant tissues (see above).

At the present time, we are conducting an investigation into which of the treatment models is the best. What this means is that patients with colon cancer who are going to have surgery are given preoperative radiation therapy and have surgery according to different schedules. One group receives radiation therapy during one week followed by immediate surgery; a second group of the same size receives the same radiation therapy but surgery is delayed by 4-6 weeks. Finally, a third group of the same size will receive radiation therapy for four weeks and surgery 6-8 weeks thereafter.

We want to know if you would like to participate in this study. If so, your treatment will be determined according to a so-called randomization process, in which the treatment you receive of the three alternatives described above is determined randomly. The radiation therapy will be administered at an oncology clinic. You will have surgery and be followed up at the surgical clinic where you had your surgery or, if you prefer, with your own doctor.

If you do not wish to participate in the study, we will suggest that you receive radiation therapy in the manner commonly prescribed today – that is, for one week followed by surgery within one week. You are completely free to decline participation in the study. If you choose to decline, this will in no way affect your care or your treatment otherwise.

If you have questions, you can consult with your surgical or oncology clinic.

For the Regional Care Program Committee for Large Intestine and Colon Cancer in the Stockholm-Gotland Region

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P.S. The Regional Care Program Group is a cooperative group consisting of physicians with special interest in the treatment of colon cancer and who are active in the Stockholm-Gotland region. All of Stockholm’s hospitals are represented in the regional care program group and treat all patients according to an established program. This study is being conducted within the context of this program.

BC/IT 98-05-13
Information for you
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By delaying surgery after completed radiation therapy by between 4-8 weeks, it is possible that at the time of surgery, the tumor will have shrunk in size thanks to the radiation therapy. If this procedure in turn reduces the risk for recurrence or affects the risk of side effects is not known. We do not know either to what extent such a reduction in tumor size would mean that more patients could be operated in such a way that the sphincter is spared and ostomy avoided without an increased risk for recurrence.

In order to try to answer these questions, we are currently conducting an investigation into which of the treatment models is preferable. What this means is that half of the patients who will have surgery for colon cancer after preoperative radiation therapy will have surgery within one week after completed radiation therapy while the other half will have surgery 4-8 weeks after completed radiation therapy.

We want to know if you would like to participate in this study. If so, your treatment will be determined according to a so-called randomization process, in which the treatment you receive of the two alternatives described above is determined randomly. The radiation therapy will be administered at an oncology clinic. You will have surgery and be followed up at the surgical clinic where you had your surgery or, if you prefer, with your own doctor.

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For the Regional Care Program Committee for Large Intestine and Colon Cancer in the Stockholm-Gotland Region

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Responsible physician
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BC/IT 99-05-04