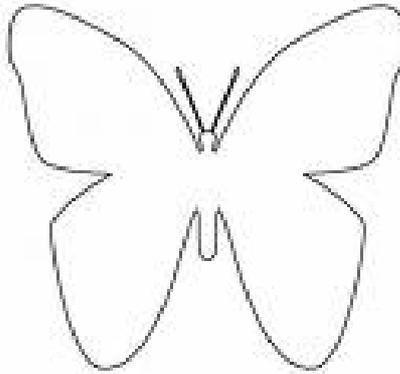


Observational study on contact X-ray and transanal endoscopic microsurgery in curative treatment of rectal cancer (CONTEM)



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Abbreviations

ASA: American Society of Anesthesiologists
CC: Concomitant chemotherapy
CRM: Circumferential margin
CRF: Case Record Form
CT: Computed tomography
CXRT: Contact X-ray
DRE: Digital rectal examination
EBRT: External beam radiotherapy
EUS: Endoscopic ultrasound
HRQoL: Health related quality of life
LE: Local excision
IMRT: Intensity Modulated Radiation Therapy
MRI: Magnetic resonance imaging
PM: Piece meal
SM: Submucosal
TAE: Transanal Excision
TEM: Transanal endoscopic microsurgery
TLE: Transanal local excision
TME: Total mesorectal excision
VSI: Venous space invasion

1. Synopsis

Aim: To evaluate outcome of definitive contact X-ray and local excision (LE) with respect to local control, disease free survival and morbidity in patients with:

- 1) T1 rectal cancer treated primarily with transanal resection (CONTEM-1)
- 2) T1 and T2 treated with primary contact X-ray or contact X-ray combined with radio-chemotherapy (CONTEM-2).
- 3) Medically inoperable patients or patients refusing total mesorectal excision with T1, T2 or early stage T3 rectal cancer treated with primary contact X-ray and external beam radiotherapy (CONTEM-3).

Endpoint:

- Primary endpoint: Local control.
- Secondary endpoint: Disease free and overall survival, morbidity and organ function.

Main inclusion criteria:

- Adenocarcinoma of the rectum.
- T1, T2 or early T3.
- Early T3 defined as:
 - Circumferential margin on MRI > 1mm.
 - Tumor extension into mesorectum on MRI \leq 5 mm.
- Largest clinical tumor diameter \leq 5 cm.
- Primary tumor within reach of contact X-ray and transanal resection.
- Circumferential tumor involvement of rectum \leq 50%.
- N0 by imaging and clinical examination.

Treatment

- *CONTEM-1* (T1)
 - Primary LE for T1 < 2 cm.
 - Postoperative treatment according to surgical margin, pathological stage and presence of venous invasion.
- *CONTEM-2* (T1-T2)
 - Primary CXRT for T1 < 2 cm and primary CXRT combined with EBRT and CC for T1 2-5 cm and T2.
 - Secondary surgery according to tumor status 6 weeks after completion of radiotherapy.
- *CONTEM-3* (T1, T2 and T3)
 - Primary CXRT for T1 < 2 cm and primary CXRT combined with EBRT (and CC if possible) for T1 2-5 cm and T2-T3.
 - Secondary surgery according to tumor status 6 weeks after completion of radiotherapy.

Statistics

150 patients will be needed in CONTEM-1 and 150 pts in CONTEM-2 to demonstrate the efficacy and safety of the treatment strategy. A safety-monitoring commission will monitor the progression of the study. For medically inoperable patients or patients refusing TME surgery at least 50 patients will be included (CONTEM-3).

2. Introduction

Conservative treatment of rectal cancer by radiotherapy with contact X-ray was established several decades ago. The treatment principles were primarily developed in France and later brought to the United States (5;8;10;21;24-26;31). Contact X-ray is today a recognized curative treatment alternative to ablative surgery especially in early stage disease (14;22). The primary prerequisite for the success of the method is patient selection and a multidisciplinary cooperation between surgeons, pathologists, radiologist and oncologist. The patients must be adequately staged and restaged to ensure a correct timing and combination of the involved radiation and surgical techniques.

Since curative radiotherapy in general requires doses of radiation that are beyond the normal tissue tolerance, special techniques are needed to obtain a sufficiently high dose to sterilize an adenocarcinoma of the rectum (9). Contact X-ray (CXRT) developed in the 1950s is therefore a cornerstone in the curative radiation approach to this disease (25). With CXRT a hand-held 50 kV tube is used to deliver radiation through a rigid proctoscope directly to the surface of the tumor. Because of the low energy involved in CXRT and the resulting sharp fall off of dose (23% at 10 mm) it is possible to deliver 80-120 Gy in 3-5 fractions spaced by 1-2 weeks with out superseding the normal tissue tolerance. Combination of CXRT with external beam radiotherapy (EBRT) given at doses of 45-50 Gy in 25 fractions is also feasible in cases where supplementary dose is needed to the deeper parts of the tumor or to potential subclinical disease in perirectal lymph nodes (13). Even interstitial brachytherapy can be used in combination with EBRT and CXRT in more advanced cases where age, co-morbidity or compliance precludes major surgery.

One of the main limitations is that the technique requires that the lower edge of the tumor is situated 10-12 cm or less from the anal verge and that the tumor does not involve more than half of the circumference. The tumor diameter should also not exceed 4-5 cm. The technique is especially well suited in elderly and frail patient since it does not require general anesthesia and can be performed on an ambulatory basis (12).

For patients with highly or moderately differentiated T1N0 disease local control can be obtained with CXRT as sole treatment in 85-90% of the patients with limited morbidity and a good sphincter function (14). Similar results can be obtained with local excision (LE) in the form of transanal local excision (TAE) or transanal endoscopic microsurgery (TEM) (6;17;18;32). Survival rates are also comparable between CXRT and LE, with 5year survival approaching 90% depending on patient selection (12). For T1 tumors LE may therefore very well be the only necessary treatment. However, adverse pathological features may necessitate postoperative radiation (22). According to the pathological risk factors predicting enhanced risk of local or nodal recurrence CXRT can be used to treat subclinical disease at the tumor bed and EBRT to electively treat the regional nodes (17;23).

For more advanced disease (T2-3,N0-1), CXRT combined with EBRT at doses in the range 45-50 Gy may produce complete clinical response in about 70% and 50% of patients with T2 and T3 disease, respectively (5;10;21;23;26). In well-staged patients, 5 year overall survival of 86% in T2 and 52% in T3 have been reported (14). Myerson and coworkers from USA have published similar results with local control obtained in 85% of patients with T2 and 56% with T3 disease, respectively (2). It may therefore be concluded that for well-selected early T2N0, contact X-ray combined with EBRT and subsequent TEM is a viable alternative to total mesorectal excision (TME). For T3 disease the results are clearly inferior to TME surgery and attempt for curative

radiotherapy should only be offered to frail elderly patients not expected to be able to sustain major surgery or to patients who absolutely refuse TME. Interstitial brachytherapy as a final boost may be an option when CXRT and EBRT and concurrent chemotherapy fails to provide complete clinical remission in such patients providing rates of local control and 5 year survival better than 60% (10).

Since the aim of this protocol is to avoid organ ablation by TME it is important to obtain maximal downsizing with the non-surgical parts of the treatment. In the recent years concurrent chemo-radiotherapy has gained acceptance as standard preoperative treatment in rectal cancer because the addition of chemotherapy significantly reduce the risk for local recurrence (1;3;11;30). The optimal chemotherapy schedule for combining with concurrent radiotherapy has so far not been determined in regular phase III studies (30). However, Recent phase I-II studies suggest that the most effective and tolerable chemotherapy regime currently is the XELOX-RT comprising Capecitabine and Oxaliplatin (7;15;20;28;30). In addition, the combination of Capecitabine and Oxaliplatin has shown the largest response rates and resection rates in patients with solid liver metastases and is also the first line regimen of choice for disseminated disease (15). Based on the available phase I-II studies Capecitabine should be administered twice daily at a dose intensity of 1300-1500 mg/m² (7;15). Higher dose levels (>1600 mg/m²) of Capecitabine given in combination with Oxaliplatin and radiotherapy have resulted in unacceptable toxicity (7). For Oxaliplatin the recommended dose intensity is in the range 5.7-7.4 mg/m² (7;15;28). Oxaliplatin has been given either at day 1 and 29 (15) or weekly at days 1, 8, (15), 22 and 29 during the 5 weeks of radiotherapy (7;20;28). Based on these data the doses selected for the XELOX-RT for this protocol will be Capecitabine 800 mg/m², twice daily, 5 days per week during radiotherapy and Oxaliplatin: 50 mg/m², given weekly. With these doses of Capecitabine and Oxaliplatin it is expected that more than 95% of the patients will be able to complete radiotherapy as planned. Less than 15% of the patients are expected to develop grade 3-4 toxicity, necessitating dose modifications of chemotherapy.

In view of the simplicity of CXRT and the obtained results it is astonishing that this method has not gained wider ground in the treatment of rectal cancer. One major hindrance is shortage of contact X-ray machines, since the manufacturer does not produce the machine anymore. However, the company Ariane Medical Systems has produced a new CXRT unit, which will create the opportunity for dissemination and further development of the technique. In addition, cooperation has been established with one of the leading French centers for CXRT to ensure a complete and correct transfer of the technique with in the frame of a scientific protocol. Thus, the aim of the present study is to evaluate the efficacy and morbidity of organ preserving treatment of early stage rectal cancer by use of contact X-ray, concomitant chemo-radiotherapy and LE.

3. Aims of the study

- 1) To institute contact X-ray as an integrated element in a comprehensive organ-conserving treatment program for early stage rectal cancer integrating transanal excision and contact X-ray further supplemented with external beam radiotherapy and concurrent chemotherapy according to predefined criteria.
- 2) To establish a homogeneous cohort of patients treated according to a strict protocol enabling a meaning full comparison of outcome with peer reviewed international results.
- 3) To obtain a prospective functional assessment of ano-rectal function following organ-conserving management of early stage rectal cancer.

4. Study design and endpoints

A prospective observational study will be performed in patients with T1-T2 and early stage T3 adenocarcinoma of the rectum. Maximal clinical tumor diameter is 5 cm and all operable patients should be N0 and M0 as judged from staging employing clinical examination, EUS and MRI. At present there is no clear radiological definition for N0, as neither size nor number of nodes correlate with histopathology. At present nodal morphology on MRI seems to be the best available radiological predictor for nodal involvement (4). A pragmatic solution has therefore to be reached. In the present protocol we will define N0 as patients who on MRI at most have 2 mesorectal nodes, none larger or equal to 10 mm and none with irregular borders or mixed signal intensity. However, DRE and EUS should also be in accord with an N0 stage.

For medically fit patients with T1-T2 disease the protocol offers an organ conserving treatment alternative to TME. This part of the study is subdivided in two according to primary treatment:

- 1) Local excision (LE): CONTEM-1
- 2) Contact X-ray (CXRT): CONTEM-2

In CONTEM-1 the primary treatment for small and well/moderately differentiated T1 tumors (< 2 cm) is LE (TEM or TAE) followed by observation, adjuvant treatment (CXRT, CXRT combined EBRT and CC) or salvage surgery (TME) according to defined risk criteria based on the pathological finding in the surgical specimen (see section 8).

In CONTEM-2 the primary treatment for small and well/moderately differentiated T1 tumors (< 2 cm) is CXRT. For larger T1 tumors measuring 2-5 cm and T2 tumors \leq 5 cm the primary treatment will be CXRT, EBRT and CC. Also low differentiated T1 < 2 cm will be treated with CXRT, EBRT and CC. Restaging will be performed 6 weeks after the primary treatment to asses whether the patient can proceed to regular follow-up or secondary surgery (TEM or TME) is needed.

Within each stratum of T-stage, the primary endpoint is local control. A local recurrence whether mural or extramural is defined as being topographically related to the site of the primary tumor in the rectum and adjacent areas in the anal canal and mesorectum (mesorectal subsite and inferior pelvic subsite) (29), and is regarded as a major adverse event that will be monitored closely by a safety monitoring commission (see section 11). A local recurrence should be confirmed by biopsy

and its topographical relation to the primary site as per above should be established. A regional recurrence is defined as being positioned in the posterior pelvic subsite or lateral pelvic subsite (29). A contiguous recurrence involving both the primary site and the pelvic subsites will be regarded as a local recurrence. Recurrences occurring in more remote sites such as the anterior pelvic subsite or beyond will be regarded as a systemic recurrence.

Secondary endpoints comprise disease free survival, overall survival, and assessment of ano-rectal function by clinical investigation (physiology and impedance planimetry), morbidity scoring and validated patient questionnaires (19).

A separate part of the study (CONTEM-3) concerns the evaluation of the use of the combined conservative approach as an attempted definitive treatment in frail elderly patients with T1 to early T3 disease not found to be able to sustain major surgery such as TME. Strict criteria for age and/or medical scores (such as ASA score) will not be applied and it will be left to the responsible surgeon to decide whether a given patients is found medically inoperable. Medically fit patients with early T3 disease who refuse TME may also be included in CONTEM-3. In this protocol early T3 will be defined as clinical tumor size ≤ 5 cm, circumferential margin on MRI of at least 1 mm and tumor not extending more than 5 mm into the mesorectal space on MRI. All patients included in CONTEM-3 should be N0 as judged by the same criteria as used in CONTEM-1 and CONTEM-2.

The primary endpoint for the CONTEM-3 cohort is local tumor control. Since TME is not an option in these patients, the safety monitoring rules will not be applied. Also it is foreseeable that age and general condition for many patients may limit the possibilities for performing the same rigid work-up and follow-up as used in CONTEM-1 and CONTEM-2. However, patients should whenever possible be followed with regard to disease free survival, overall survival and morbidity as described in section 5 and 9.

Patients with large T3 tumors, N1 and/or limited M1 disease and in a good general condition who are treated according to the CONTEM-3 protocol can be registered in the database, but will not be included in the CONTEM-3 analysis.

5. Staging and patient work-up

All examination must be completed before treatment and no investigations should be more than 4 weeks old at time of treatment initiation. If a cancer is diagnosed following local excision for a “benign polyp” the patient can enter into the study provided that full staging according the protocol is done.

The following procedures should be performed:

- Clinical examination
- Digital rectal examination
- Rigid rectoscopy
- Tattoo of the most proximal, distal and lateral (left and right) tumor margins (optional)
- Biopsy
- Blood chemistry
- EUS
- MRI pelvis

- CT or PET-CT of thorax, abdomen and pelvis
- Morbidity scoring
- Questionnaires
- Anorectal physiology (*optional*)

Morbidity scoring is obligatory and will be performed according to CTC v. 3.0. Patient questionnaires are also obligatory and will include validated systems specific for rectal function and HR-QoL. The functional anorectal examinations are an optional element of the protocol.

For patients treated with primary CXRT ± EBRT and CC, restaging should be performed 6 weeks following completion of radiotherapy. Complete remission should always be confirmed by a negative biopsy. The restaging procedures should at least include the following investigations:

- Clinical examination with biopsy if CR
- Digital rectal examination
- Rigid rectoscopy
- Blood chemistry
- EUS
- MRI pelvis
- CT or PET-CT (optional)

6. Inclusion criteria

6.1 Inclusion criteria for CONTEM-1

- T1 rectal cancer < 2 cm measured by both rectoscopy and MRI
- N0
- Histologically confirmed high or moderately differentiated adenocarcinoma
- ASA score 1-2 and WHO score 0-2.
- No prior or concurrent second malignant tumors, except adequately treated in situ carcinoma of the cervix or basal cell carcinoma.
- Acceptable bone marrow function (leukocytes $\geq 3.0 \times 10^9/L$ and platelet count $100 \times 10^9/L$).
- Sufficient kidney function with calculated (Cockcroft-Gault) GFR > 50 ml/min.
- Acceptable liver function with normal bilirubin.
- No grade 2 (CTC v.3.0) or greater pre-existing peripheral neuropathy (motor or sensory);

6.2 Inclusion criteria for CONTEM-2

- T1 or T2 rectal cancer ≤ 5 cm measured by both rectoscopy and MRI
- N0
- Histologically confirmed high or moderately differentiated adenocarcinoma. Low differentiated T1 and T2 tumors may be included for treatment with CXRT, EBRT and CC
- ASA score 1-2 and WHO score 0-2.
- No prior or concurrent second malignant tumors, except adequately treated in situ carcinoma of the cervix or basal cell carcinoma.
- Acceptable bone marrow function (leukocytes $\geq 3.0 \times 10^9/L$ and platelet count $100 \times 10^9/L$).
- Sufficient kidney function with calculated (Cockcroft-Gault) GFR > 50 ml/min.
- Acceptable liver function with normal bilirubin.

- No grade 2 (CTC v.3.0) or greater pre-existing peripheral neuropathy (motor or sensory);

6.3 Inclusion criteria for CONTEM-3

- T1, T2 or T3 histologically confirmed adenocarcinoma of the rectum
- N0
- Medically inoperable with regard to TME or patient refusing TME.
- For T3 the inclusion also requires that:
 - MRI-CM >1 mm.
 - Tumor extension in mesorectum \leq 5 mm.

6.4 Exclusion criteria for all CONTEM protocols

- Maximal tumor diameter > 5 cm.
- Primary tumor not within reach of CXRT and LE.
- Circumferential tumor involvement > 50%.
- Nodal disease suspected or established based on the staging investigations performed.
- Concomitant administration of other antineoplastic agents.
- Psychiatric disorders or other conditions rendering patients incapable of complying with the requirements of the protocol.
- Active infection or other condition endangering treatment delivery.
- Patients for whom regular follow-up attendance is impossible are not eligible.
- Failure to obtain a negative pregnancy test in patients with childbearing potential or non-compliance with regard to use an effective method of contraception (hormonal anticonception or intrauterine device).
- No written informed consent according to ICH/EU GCP guidelines and regional and national law.

7. Treatment procedures

7.1 Local excision (LE)

TEM is the primary treatment procedure for LE. However, TLE or mucosectomy is also allowed in CONTEM-1 if TEM is not available. Full wall thickness removal with primary suture of the defect is standard for TEM. The lateral surgical margin should be 1 cm to tumor or in case of partial or complete remission on preoperative treatment, 1 cm to the tattoo marked tumor bed.

7.2 Contact X-ray (CXRT)

CXRT will primarily be performed with the patient in the knee-chest position. If the tumor is located to the distal posterior rectal wall the patients may be treated in supine position. Local anesthetics such as peri-rectal injection of lidocaine 2% can be used if necessary. After digital rectal examination the treatment proctoscope (\varnothing 2.5-3.0 cm) is introduced and the tumor area/bed is inspected. The CXRT treatment is then guided by the eye and coned to the tumor area/bed in one or more neighboring segments to cover the target with a margin of 0-3 mm.

CXRT will be used in 3 situations:

- CXRT₁: As a boost 5-6 weeks after LE of T1 tumors when pathology reveals R1 resection (i.e. surgical margin \leq 2 mm), or the tumor has been removed by piecemeal resection. The

dose delivered to the surface of the tumor bed will be 45 Gy given in 3 fractions given over 3 weeks (day 1, day 8 and day 22).

- CXRT₂: As postoperative treatment 5-6 weeks after LE for a clinically staged T1 when pathology reveals pT2 or VSI. The dose delivered to the surface of the tumor bed will be 30 Gy in 2 fractions one week apart (day 1, day 8). CXRT₂ should be followed EBRT initiated on day 15. If possible chemotherapy should be administered concomitantly with EBRT.
- CXRT₃: As primary treatment in patients with T1-T3 tumors. The dose delivered to the surface of the tumor will be 90 Gy in 3 fractions given on d1, d8 and d22. Dose of CXRT in the 2nd. And 3rd. fraction should be reduced to 15 Gy if complete remission is obtained or coned down if tumor regression allows smaller diameter than initially applied. A fourth fraction of 20 Gy may be given as boost if the tumor response is not satisfactory. As an alternative interstitial brachytherapy may be used according to institutional practice.

7.3 External beam radiotherapy (EBRT)

Treatment planning must be performed on a 3D dose planning system based on 3D CT data set. Fixation is mandatory. Normally the patient should be lying in prone position using the belly board. Supine position can be used if the patient cannot tolerate the prone position. To minimize internal motion it is important that bladder and rectum is empty both at the time of dose planning CT and at each daily EBRT fraction.

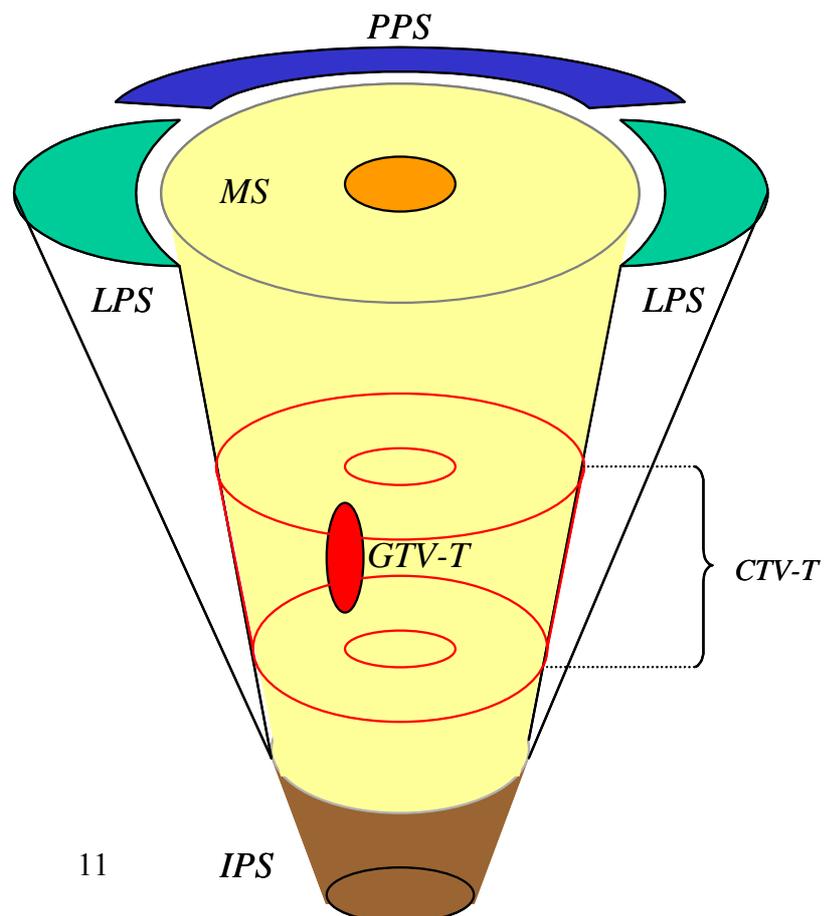
The following volumes of interest (VOI) should be defined according to ICRU62:

- *Tumor target (CONTEM-2 and CONTEM-3 only):*

- GTV-T: Macroscopic extension of primary tumor, including any additional clinical and radiological information such as MRI.
- CTV-T: GTV-T + whole mesorectum at the level of GTV with a margin of 1 cm to GTV-T in the cranio-caudal direction.
- ITV-T: CTV-T + 5 mm in both the anterior and posterior direction.
- PTV-T: Approximately 5 mm in all directions

- *Elective target:*

- CTV-E: ITV-T plus the complete mesorectal (MS), posterior pelvic



subsite (PPS) and lateral pelvic subsite (LPS) should be included (29). The external iliac and common iliac nodes should not be included. The anal sphincter should be spared as much as possible and the anal canal must be excluded completely for tumours with a margin > 6 cm to the anal verge. Therefore, the inferior pelvic subsite (IPS) should only be included to the extent that the margin to ITV-T is respected with a margin of 2 cm in the caudal direction.

- ITV-E: CTV-E + 0 mm.
 - PTV-E: Approximately 5 mm in all directions
- *Organs at risk:*
 - Bladder: Only the outer bladder wall is to be contoured.
 - Anal sphincter: Complete sphincter should be contoured
 - Rectum: The outer rectal wall is to be contoured from above the anal sphincter to the level of transition into the sigmoid.

Dose and fractionation of EBRT should be as follows:

- *CONTEM-1:*
 - PTV-E: 44-46Gy
- *CONTEM-2:*
 - o PTV-T: 50-52 Gy.
 - PTV-E: 44-46 Gy.
- *CONTEM-3*
 - o PTV-T: 50-52 Gy
 - o PTV-E: 44-46 Gy
 - o Alternatively both PTV-T and PTV-E may be treated with 25 Gy in 5 fractions

Dose per fraction for long course EBRT should be 1.8-2.0 Gy. Overall treatment time is then 5 weeks.

The biological equivalent dose in 2 gray fractions (EDQ2) for the different fraction schedules' suggested for the EBRT:

Parameter						
Total dose	25	44	45	46	50	52
No of fx	5	22	25	26	25	26
Dose/fx	5	2.00	1.80	1.77	2.00	2.00
EQD2 a/b=10	31.3	44.0	44.3	45.1	50	52

All beams and segments involved in a given part of the treatment must be treated at each fraction. The dose in each PTV should in general be within 95-107% of the prescribed dose. However, it is allowed that 1% of any PTV may receive between 90-95% of the prescribed dose. Size and position of discrete volumes receiving more than 107% of the prescribed EBRT dose should be evaluated individually and should never exceed a spherical volume with a diameter larger than 15 mm.

The following technique should normally be used for EBRT:

- Iso-centric technique, normally a combination of lateral opposed fields and a posterior field for the elective target. IMRT is allowed. A simultaneous integrated boost can be used for the tumor target if necessary.
- Beam shaping should be individualized according to target definitions by use of MLC.
- The edge of beams used to cover PTV-T in T3 disease should be set with no margin for penumbra, as PTV-T is included in PTV-E.
- Bladder and rectum should be empty before irradiation unless bladder and rectum volume is controlled by other methods.

7.4 Chemotherapy

Unless the condition of the patient precludes the use of chemotherapy, all patients receiving EBRT will also be treated with concurrent chemotherapy. Concurrent chemotherapy will not be used in medically inoperable patients.

- Capecitabine: 800 mg/m², twice daily with 12 h interval, given orally and continuously on days with EBRT, i.e. not in the weekend.
- Oxaliplatin: 50 mg/m², given weekly during radiotherapy with 2h intravenous infusion scheduled at day 1, 8, 15, 22 and 29.

The initial schedule is always combination chemotherapy, but if the patient cannot tolerate Oxaliplatin it is allowed to use Capecitabine only.

Rules for toxicity and dose reductions of chemotherapy will be adopted from Rödel et al (28). Patients will be evaluated weekly during preoperative treatment with toxicity scoring, clinical investigation and blood tests.

Concurrent chemotherapy with both Capecitabine and Oxaliplatin is abandoned for any grade-4 toxicity. In patients experiencing any grade-3 toxicity treatments with both Capecitabine and Oxaliplatin should be interrupted but may be resumed in 75% of the original dose when the toxicity is resolved to grade 0 or 1 at first appearance and 50% of the starting dose at second appearance. However, Capecitabine should always be reduced to 50% in patients who experience grade 2 hand-foot syndrome. Oxaliplatin should be withheld in patients developing grade 2-3 neuropathy until recovery to grade 0-1 and then resumed in 75% of the original dose after grade 2 and 50% after grade 3. Dose of both Oxaliplatin and Capecitabine should be reduced to 75%, 50% or 0% if the weekly measurement of the total white blood count is $< 3.0 \cdot 10^9/l$, $< 2.5 \cdot 10^9/l$ or $< 2.0 \cdot 10^9/l$.

7.5 Total mesorectal excision (TME)

TME will be used as in case of insufficient clinical or pathological response or as salvage treatment in case of a local recurrence in medically fit patients. In this protocol insufficient regression will be defined as clinical tumor diameter ≥ 2 cm evaluated by rigid rectoscopy 6 weeks after primary radio-chemotherapy. Insufficient pathological response as evaluated by the TEM specimen is defined as: pN1, pT3 or R1 (resection margin ≤ 2 mm). The TME procedure will be performed according to Heald (16) and the pathological evaluation of the operative specimen according to Quirke (27).

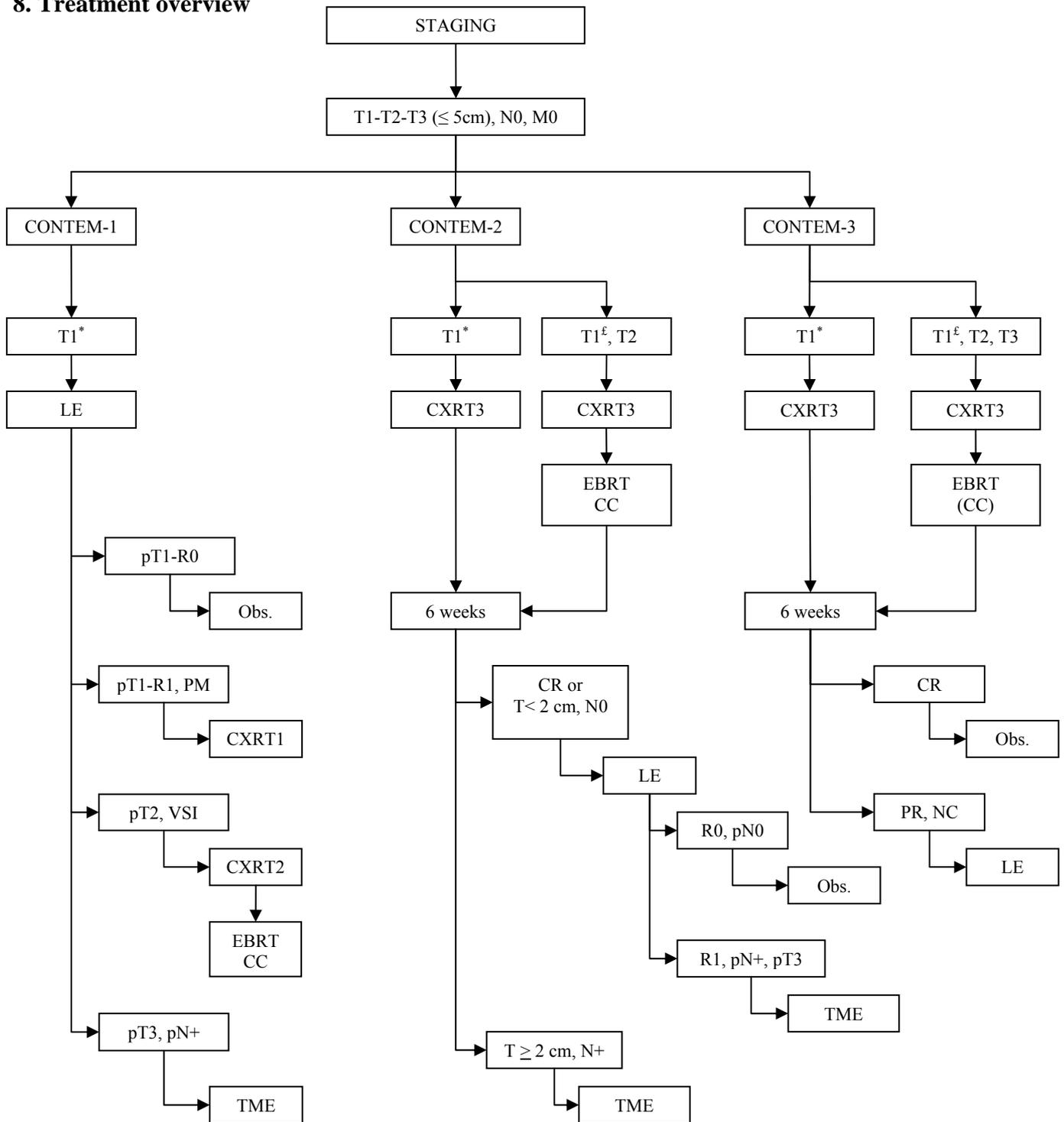
7.6. Supportive and concomitant treatments

Patients should receive full supportive care including transfusion of blood and blood products, antibiotics, anti-diarrhoeals and analgesics as appropriate.

Patients may not receive non-protocol anti-cancer therapy (hormonal, cytotoxic, biological) while participating in this study and should not receive any non-protocol anti-neoplastic treatment until disease progression.

Patients with incurable local or disseminated disease will go off study and will be treated with palliative intent by the discretion of the involved physicians.

8. Treatment overview



*Well/moderately differentiated and tumor size < 2 cm

^fLow differentiated or tumor size 2-5 cm

CXRT1: 45 Gy/3 fractions, day 1, 8 and 22

CXRT2: 30 Gy/2 fractions, day 1 and 8

CXRT3: 90 Gy/3 fractions, day 1, 8 and 22.

EBRT: 45-50/25 fractions, initiated day 15

CC: Concomitant chemotherapy

9. Follow-up investigations

The involved surgeons and oncologist will jointly perform follow-up at 3-60 month according to this table:

Time after treatment	3	6	9	12	15	18	21	24	30	36	48	60
Clinical examination	●	●	●	●	●	●	●	●	●	●	●	●
Digital rectal examination	●	●	●	●	●	●	●	●	●	●	●	●
Rectoscopy	●	●	●	●	●	●	●	●	●	●	●	●
EUS	●			●				●		●		
MRI pelvis	●			●				●		●		
CT thorax, abdomen & pelvis	●			●				●		●		
Morbidity scoring	●	●		●		●		●		●	●	●
Functional anorectal assesment		●		●				●				●

In case of suspected recurrence a complete patient work-up must always be performed including digital rectal examination in GA, MRI, and CT thorax, abdomen and pelvis. It is allowed to replace CT with PET-CT. All recurrences must be verified by biopsy.

10. Assesment of ano-rectal function and morbidity

The assessment of the anorectal function will be performed systematically both before treatment and during follow-up for patients recruited in CONTEM-1. The assessment should at least involve morbidity scoring and questionnaires. Departments participating in the optional extended evaluation will also perform impedance planimetry and anorectal physiology testing.

Scoring of anorectal morbidity will be performed using CTCv3.0. Morbidity from the patients perspective will be evaluated by standardized and validated questionnaires. Questions regarding urinary and sexual function will be included. Furthermore questionnaires assessing quality of life will be used.

Rectal impedance planimetry allows a detailed description of anorectal motility. The system measures the rectal cross-sectional area (CSA) under luminal pressure loading of a fluid-filled balloon. The system is based on measurements of electrical impedance of saline inside a balloon. Five pairs of detection electrodes are mounted between two excitation electrodes on a 18 cm long probe. The probe and the electrodes are covered with a non-compliant flaccid bag of polyurethane. The bag is filled and emptied with electrically conducting fluid through a central channel with several side holes. The excitation electrodes are connected to a generator in the impedance planimeter (Gatehouse, Noerresundby, Denmark). The electric potential difference between the two electrodes in a pair is measured by connecting the electrodes to an impedancemeter measuring the potential difference between them. A converter transforms the potentials into CSAs. The pressure is measured using a low-compliance system with an external transducer (Baxter, California, USA). Infusion of 0,018 % NaCl through the infusion channels distends the balloon. The height of a level container determines the applied balloon pressure. Rectal impedance planimetry system allows simultaneous measurement of luminal CSA at several levels in the rectum and rectoanal pressures and has several advantages to previous methods used for rectoanal motility and physiology.

Manometry and measurement of rectal sensation will be used to evaluate anorectal physiology. A manometric system (Medtronic) will be used. Two open-ended lubricated catheters are introduced manually into the rectum: one catheter monitoring the rectal pressure, the other the anal pressure. The maximum resting pressure (MRP) is measured by retracting the anal pressure catheter through the sphincter zone. The patient is asked to squeeze maximally without activating the abdominal musculature. Maximum increase of pressure over basal pressure is recorded as the maximum squeeze pressure (MSP). For both MRP and MSP, three consecutive recordings are obtained, and the mean value is charted. To measure rectal sensation a collapsed, high-compliance balloon mounted on a catheter is introduced manually into the rectum. The distal end of the balloon is placed just above the anal canal. The rectal balloon is distended by continuous infusion of distilled water. The patient is instructed to report when (s)he first feels 1) distension of the rectum, which is recorded as the minimum perceived volume (MPV), 2) a desire to defecate (DD), and 3) urgency, when the DD becomes urgent (U).

Endoanal ultrasonography: An Endosonic 360° Axial Transducer is used to identify the internal and external sphincter. The probe is inserted into the anal canal and withdrawn slowly until the sling of the puborectalis is identified. The sphincters will be investigated by moving the probe slowly through the canal.

11. Statistics

A local recurrence is a serious event that may be unsalvageable. A rate of local recurrences of more than 8% in population of patients where the standard treatment most likely would have been surgical treatment with TME is therefore considered unacceptable in this trial. Assuming that the true actuarial incidence of local recurrences is 2% at 5 years we will power the study to be able to reject that this rate is 8% or more.

For a test of a binomial proportion using the normal approximation with a one-sided significance level of 0.025 and null proportion 0.08, an approximate sample size of 118 achieves a power of at least 0.8 when the true proportion is 0.02. The approximate power is 0.804. To guard against loss of patients during follow-up we will aim for a recruitment of at least 150 patients.

The Department of Clinical Epidemiology, Aarhus University Hospital will monitor the progression of the study and will activate an independent data-monitoring committee in the event that an extramural local recurrence has been reported.

After the analysis of the data, the involved investigators will be informed and the relevant ethical committees will be requested to judge the proposal of the safety-monitoring commission, based on the results of this analysis, regarding:

- a) the closure of the study, or
- b) the progression of the study with an amended protocol, or
- c) the progression of the study with an unchanged protocol.

In addition to the continuing monitoring of the study and interim analysis should be performed when 50 patients with T1-T2 tumors have been treated and followed for at least 12 month. If the

interim analysis reveals one or more of the following serious adverse events the protocol will be suspended:

- Local recurrence rate > 20%
- Treatment related mortality > 4%
- Severe local morbidity Grade 4 (CTC v3.0) > 10%
- Salvage TME rate > 50%

For patients accrued in the protocol on the background of being medical inoperable or not being willing to undertake TME surgery, we will accumulate at least 50 patients and follow them for at least one year before analyzing and publishing the results. Since these patients are treated in the protocol with no available treatment alternative the safety-monitoring commission will not monitor them.

For all 3 CONTEM studies the accrual and registration in the database will continue as long as possible and serve as a continuing surveillance of the use of CXRT. Thus, there is at the moment no upper limit as to the number of patients that will be included in the study.

12. Patient registration procedure

Patient's registration will only be accepted from authorized investigators. The patient registration will take place over the Internet via a server placed at Aarhus University Hospital, Denmark. The server contains a registration programme, which each centre will gain access to via a username and password. When logging on to the CONTEM site, each centre must key patient data on patients, who have given their consent and who fulfil the inclusion criteria for the study. The data is encrypted before the information is transmitted over the Internet

Patients must be registered before any treatment procedures are initiated. A list of questions to be answered during the registration procedure is included in the registration check-list, which is part of the case report forms.

- Name of the responsible investigator
- Patient's initials
- Patient's birthday (dd.mm.yyyy)
- Eligibility criteria will be checked
- Date of scheduled treatment start

At the end of the registration procedure, a unique number will be allocated to the patient (patient sequential identification number) who will identify the patient in relation to all future communication between the database and the investigator.

13. Data forms and procedures for data collection

Patient data will be collected in standard CRF's via the Internet. Identification will be by patient sequential study number and patient initials. A database for the project will be established, and placed at Aarhus University Hospital, Denmark. The Danish Board of Registry has approved the database. Access to the database can be gained through the project's homepage, by providing a

valid username and password. Keying of baseline- and follow-up data will be carried out over the Internet using a standard web-browser. A number of validation procedures will be installed in order to ensure a high data quality. Reminders will be sent out for all follow-up visits and examinations, and data from these will also be keyed via the Internet. Each centre will be able to log on to the database via the homepage at any time in order to see descriptive data and number of included patients for own centre as well as for the entire study population. Individual patient data are only available to the principal investigators at each participating institution.

CRF's must be entered via the Internet as soon as the requested information is available, according to the schedule described below. It is the responsibility of the investigator to check that all CRF's have been sent to the database and that they are completely and correctly filled out. Investigator should keep a copy of his or her own CRF for each registered patient.

The following schedule for CRF reporting will be used:

- Registration form: To be completed before treatment
- On study form: To be completed within 4 weeks after treatment initiation
- Baseline morbidity form: To be completed within 4 weeks after treatment initiation
- CONTEM Treatment forms (1,2 or 3): To be completed within 4 weeks after treatment completion
- Follow-up form: To be completed within 4 weeks after each follow-up
- Off study form: To be completed within 4 weeks after documented recurrence or death

14. Ethical considerations

14.1 Patient protection

The investigators will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West and Edinburgh amendments) or the laws and regulations of the country, whichever provides the greatest protection of the patient. The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice. The protocol will be approved by the Regional Ethics Committee.

14.2. Subject identification

The name of the patient will not be asked for nor recorded at the Data Center. A sequential identification number will be automatically attributed to each patient registered in the trial. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, patient's initials (maximum of 4 letters), date of birth and local chart number (if available) will also be reported on the case report forms.

14.3. Informed consent

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed.

They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating

physician. An example of a patient informed consent statement is given as an appendix to this protocol.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered at the Data Center. This must be done in accordance with the national and local regulatory requirements.

For European Union member states, the informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that "the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative".

14.4. Advantages and disadvantage for the patients

At present the standard treatment for patients with localized rectal cancer is most often TME surgery. This operation involves some risk of operation mortality and long-term morbidity. Based on peer reviewed data, the conservative treatment approach, which forms the basis for this protocol, will provide them with a treatment alternative that to a higher degree is expected to ensure both local control and good functionality.

Patients with localized rectal cancer considered medically inoperable due to concurrent disease and age or patients who refuse TME surgery are today treated in a non-standardized manner, which span from attempted radical treatment by surgery by TEM to radiotherapy. Due to the limited possibilities for delivering a sufficient dose of radiation to the primary tumor with conventional radiation techniques, these patients often do not obtain local control. Patients included in the protocol will have the advantage that they will be offered additional treatment modalities such as CXRT in an ordered and preplanned manner which based on the available data is expected to ensure a higher level of local control with an acceptable level of morbidity, than these patients can achieve with non-standardized approaches.

The patients will be fully informed about the background for the study and that conservative treatment based on CXRT and TEM is a new treatment option. The patients will be informed about the possible risks and side effects connected to the involved treatments. They will also be informed that a safety-monitoring commission is supervising the study with regard to occurrence of extramural recurrences. If they do not wish to participate, this will not prevent them from obtaining other treatment. On this background it seems reasonable to conduct the investigations and the potential benefits will be greater than the potential drawbacks (risk of recurrence which is not salvageable).

Should patients with T1-T2 rectal cancer decide not to participate in the protocol they will as a rule be offered treatment with TME. Medically in inoperable patients or patients who refuse TME surgery will be treated as best as possible on an individualized basis at the discretion of the responsible physician.

15. Publication of data

The study coordinator will prepare the primary articles concerning the clinical subject of the project and will be the first author. All papers and abstracts will be co-authored by the national coordinators

of the CONTEM protocol according to the Vancouver rules. Investigators from institutions contributing at least 10% of the included patients will also qualify for co-authorship.

Any investigator can prepare presentations at meetings, companion papers based on secondary analysis or based on data from his/hers own institution. However, approval is required in advance from the CONTEM group prior to submission in all cases.

16. The CONTEM group

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Website: www.contem.dk (not activated yet)

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