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ORIGINAL ARTICLE

Long-term results of a phase II trial of high-dose radiotherapy (60 Gy) and UFT/l-leucovorin in patients with non-resectable locally advanced rectal cancer (LARC)

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Abstract

Background. Preoperative radiochemotherapy is a cornerstone in patients with non- resectable locally advanced rectal cancer (LARC). To improve outcome (number of R0 resections and survival) high-dose radiotherapy (RT) was combined with oral UFT/l-leucovorin to allow tumour regression before radical intended surgery. *Methods.* Pelvic RT was delivered with megavoltage photons using a 5 field technique. RT was CT-based, given 5 days a week through one posterior field and two lateral fields (48.6 Gy/27 fractions) to encompass the primary tumour and the regional lymph nodes. In addition, the tumour bed received a concurrent boost (5.4 Gy/27 fractions) and a final boost (6 Gy/3 fractions); thus GTV received 60 Gy/30 fractions. Concurrent with RT patients received a daily dose of oral UFT 300 mg/m^2 plus l-leucovorin 22.5 mg 5/7days (divided in three doses). *Results.* From September 2000 to November 2004, 52 patients (median age 60 years (32–83); median PS 0 (0–2)) with LARC (36 primary, 16 recurrent) were included in this phase II study. All but three patients received the planned 60 Gy, median duration of RT was 42 days (25–49). Toxicity was very modest; only four patients had a dose reduction of UFT. No hematological toxicity of clinical significance was seen. Non-hematological toxicity grade 1 (GI-toxicity, fatigue and/or dysuria) was frequently observed but only four patients experienced grade 3 toxicity (diarrhoea and/or nausea/vomiting). Forty patients (77%) were operated (30 R0, 5 R1, 5 R2) median 55 days (27–112) after completion of RT. Seven (13%) patients had a pathological complete response (pCR). Thirty-one patients (60%) died after median 25.4 months (1.6–45.2 months). Twenty-one patients (40%) are still alive June 2007. *Conclusions.* Preoperative high-dose RT and concomitant UFT produces major regression in most patients with non-resectable LARC and thus a good chance of cure.

At diagnosis rectal cancer (RC) has different patterns of presentation, which greatly influences both the prognosis and treatment choices. RC is frequently diagnosed at a stage when complete resection is possible. However, because of distant metastases or local recurrence, only half of the patients who undergo surgery will be cured. After conventional resection, local recurrence rates of 25 to 40% have been reported. Advances in the treatment of rectal cancer, such as total mesorectal excision (TME) but also the use of pre- or postoperative radiotherapy (RT) or radiochemotherapy (RCT), have substantially reduced the incidence of local recurrence and increased survival [1].

Approximately 10% of the patients present with a locally advanced non-resectable tumour (LARC) without possibility of a simple en-bloc resection but without distant metastases at the time of diagnosis. Local recurrences can be non-resectable as well, and the two categories are often treated the same way. Uncontrolled LARC is accompanied by severe suffering for the patient, with pain as the most common symptom, and the prognosis is poor with a median survival of 9–18 months [2].

During the past decade adjuvant RT alone or in combination with chemotherapy has been used more frequently in resectable RC. The aims of preoperative treatment are to reduce the local recurrence rate,

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to improve survival, to increase the chance of a sphincter-sparing resection in low-lying cancers, to cause down-staging and finally to cure patients in which resection is not otherwise possible [3].

Concomitant RCT with 5-fluorouracil (5-FU) as the drug of choice probably improves the effect and increases the chance of complete pathological remission (pCR) [3,4]. Concomitant infusion of 5-FU (CVI) is better than bolus infusion [5].

UFT is an oral formulation of the prodrug tegafur and uracil. Tegafur is converted to 5-FU primarily in the liver and uracil inhibits the degradation of 5-FU. The use of UFT is convenient without the necessity of a central venous catheter and the plasma concentrations of 5-FU on UFT treatment given in a 5/7 days schedule mimics that of CVI [6].

Several radiotherapy schedules have been used in preoperative studies. In the absence of randomised trials comparing different radiation schedules, it is not possible to define the most optimal preoperative treatment. However, long-course RT (45–60 Gy) can cause tumour regressions allowing subsequent radical surgery in 40–80% of the patients with LARC giving 20–30% long-term survivors [3].

Apparently there exists a dose-response relationship resulting in a better tumour response with a higher dose of radiation [7–9].

A phase I trial with preoperative high-dose RT (60 Gy in 30 fractions using concomitant boost techniques) and concurrent oral UFT/l-leucovorin (Lv) to patients with non-resectable rectal cancer (primary and recurrent) showed promising efficacy and toxicity profile [10], and here we present the subsequent phase II trial in 52 patients with non-resectable LARC.

The primary end-point of the present study was to assess efficacy (number of R0 resections) and the secondary end-points were to determine the number of patients with pCR, overall survival (OS) and toxicity.

Material and methods

Criteria of eligibility

All patients had biopsy-proven non-resectable (primary or recurrent) rectal carcinoma (LARC). Patients were eligible if the tumor was fixed to the pelvic wall or otherwise non-resectable as judged clinically by an experienced colorectal surgeon. Patients were required to have a WHO performance status 0–2, age >18 years and adequate bone marrow, renal and hepatic function (WBC $>3\times10^9$/l, platelet count $>100\times10^9$/l, total bilirubin level $<1.5\times$ upper normal value and creatinine <150 mol/l).

The exclusion criteria were extrapelvic disease, prior adjuvant chemotherapy with 5-FU within 12 months, previous pelvic irradiation, laparotomy within 2 weeks before inclusion, prior or concomitant malignant disease or pregnant or lactating women.

Investigations and follow-up

Pretreatment investigations included a complete medical history, blood chemistry, physical examination, WHO performance status, weight and chest x-ray. Pelvic and abdominal CT-scans were performed to supplement the clinically judgment of non-resectability and to outrule extrapelvic disease. MR-scan was not part of the routine investigations when the study started.

Performance, weight and blood tests were evaluated every 2 weeks during RCT.

Overall survival time was estimated as the time from registration until death from any reason or the last date of follow-up. The number of patients with pathological complete remission was judged by an experienced colorectal pathologist.

Ethics

The protocol and the procedures followed were according to the Helsinki Declaration and were approved by the regional and national Ethical Committee.

Radiotherapy

RT was delivered 5 days a week, once a day, to a total dose of 60 Gy in 30 fractions to the primary tumour. This was accomplished using 27 fractions of 1.8 Gy to the pelvis with a concomitant boost of 27 fractions of 0.2 Gy to the primary tumour, and a final boost of 3 fractions of 2.0 Gy. Macroscopically identified tumour tissue (GTV) included the primary tumour and other macroscopically identified tumour. GTV was defined by integrated information obtained by CT- or MR-scan and/or any clinical information. The clinical target volume (CTV) was defined as GTV plus tissue harbouring potential microscopic disease including presacral and perirectal areas with lymph nodes as well as internal iliac lymph nodes. The upper border of the radiation portals was the promontorium (the junction L5-S1) and the lower was 3 cm below the primary tumour or 1 cm below the obturator foramen. If there was distal extension of the tumour to the anal verge, the perineum was included. All patients were treated supine using high-energy megavoltage linear accelerator. A 5-beam technique with concomitant boost was used. A posterior (field 1) and two lateral fields (fields 2

and 3) encompassed CTV (1.8 Gy/day) and, as concomitant boost, two lateral boost portals (fields 4 and 5) encompassed GTV with a 1-cm margin (0.2 Gy/day). The two lateral boost portals were also used for a final 6 Gy boost (2.0 Gy/day). CTV thus received 48.6 Gy in 27 fractions and GTV received 60 Gy in 30 fractions. The prescribed dose to GTV was specified according to ICRU 50 and 62 with the isodose distribution to the GTV of at least 95%. All five fields were treated in the same session.

Chemotherapy

Concurrent with RT patients received oral UFT 300 mg/m^2/day, 5 days a week for 30 days, divided in three daily doses plus a fixed dose of l-leucovorin 7.5 mg (22.5 mg daily) with each UFT dose.

Toxicity

Toxicity was graded according to NCI Common Toxicity Criteria version 2.0 and evaluated every 2 weeks during the course of radiation and 3 weeks after completion of treatment.

Antiemetic and antidiarrhoeal drugs were not offered prophylactically but could be used when needed.

Evaluation of response

The tumour response and resectability was evaluated with digital rectal examination by an experienced colorectal surgeon and an abdominal CT- or MR-scan 4 weeks after completing the treatment. Laparatomy and intended radical resection was planned 6 weeks after the completion of RCT in the absence of progression. The final judgment of resectability was clinical.

The operation was classified either as R0 if the resection margin examined by the pathologist was uninvolved, R1 (macroscopic radical) or R2 if macroscopic tumour remained in the operative field at the end of the surgical procedure. The same experienced pathologist evaluated specimens for pathological complete response.

Statistical evaluation

Non-parametric statistics were applied. All median values are followed by range in brackets. Overall survival curves were generated according to the Kaplan-Meier method. OS were updated until June 1, 2007.

Results

From September 2000 to November 2004, 52 patients (32 men and 20 women) were treated according to this phase II trial. Median age was 60 years (range 32–83 years) and median performance status was 0 (0–2). Thirty-six patients had primary non-resectable RC and 16 patients had recurrent non-resectable pelvic disease.

All except three patients received the preoperative 60 Gy in 30 fractions. One patient terminated RT prematurely after 46 Gy due to severe gastroenteritis complicated with endocarditis, one patient died due to peritonitis after having a gastrostomy feeding tube inserted and finally one patient died due to a lung embolus. The median duration of RT was 42 days (range 25–49 days). Forty-eight patients received the planned dose of UFT. Four patients had dose reduction of UFT/Lv (median dose 75%) primarily due to gastrointestinal toxicity.

Table I shows acute toxicity associated with preoperative RCT. No clinical significant hematological toxicity was observed. Only four patients experienced grade 3 toxicity (primarily diarrhoea and/or nausea/vomiting).

Surgery was performed in 39 patients (75%) median 55 days (range 27–112) after completion of RT. The type of surgery is shown in Table II. Thirty patients (58%) had microscopic radical surgery (R0), five patients had R1 resection and four patients only had R2 resection. Seven patients (13%) had pCR. Thirteen patients had no surgery (including two patients who died before surgery), ten patients still had clinical non-resectable disease and one patient developed extrapelvic disease after completion of RCT but before surgery.

Postoperative therapy was not part of this protocol.

Overall survival for all 52 patients is shown in Figure 1, survival at 5 year was 39% (27–50%). In 30 patients having R0 resection 5 year survival was 62%. The patients who did not have R0 resection

Table I. Incidence and toxicity grade (CTC) in 52 patients treated with RCT.

Grade	0 %	1 %	2 %	3 %
Nausea/vomiting	61	23	10	6
Diarrhea	38	46	12	4
Stomatitis	94	6	0	0
Dysuria	86	11	3	0
Pain	93	2	5	0
Skin reaction	92	8	0	0
Hematological	98	2	0	0

Table II. Type of surgery in 52 patients according to primary or recurrent disease.

	All	Primary	Recurrent
n	52	36	16
Hartman	10	9	1
LAR	10	7	3
APR	17	11	6
Laparatomy only	2	2	0
No operation	13	7	6

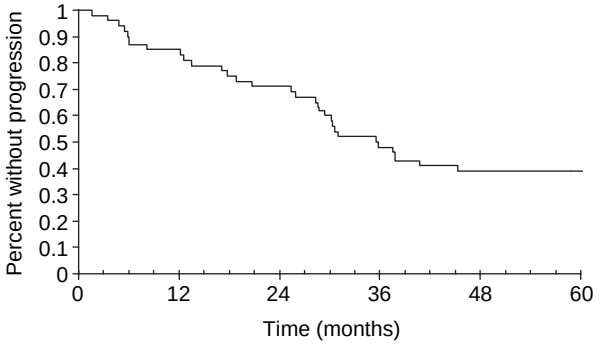

Figure 1. Kaplan-Meier curve of overall survival for 52 patients with non-resectable LARC.

had a median overall survival of 18.8 months. In patients with primary RC, 46% were alive at 5 years but only 25% of patients with recurrent disease. However, there was no clear difference for patients having R0 resection (5 years survival was 66% for 22 patients with primary RC and 50% for 8 patients with recurrent disease).

Discussion

Patients with resectable rectal cancer benefit from peroperative adjuvant RT in terms of local failure and survival. Preoperative RT (with or without chemotherapy) is more effective than postoperative therapy [1]. Adding chemotherapy to preoperative RT decrease LRR and induce pCR in 10 to 30% [1] but at the moment it has not been shown that survival is improved [11,12].

Both short- and long-term RT reduce local recurrence rates (LRR) in patients with resectable RC but only long-term RT produces tumour regression and short-term RT can therefore not be used in patients with LARC [13]. Combining radiotherapy and chemotherapy in these patients can produce tumour shrinkage with subsequent radical surgery in more than 50% [14]. Thus, the evidence is only indirect that RCT is superior to RT alone. In the last more than ten years there has not been published phase III data concerning this item in patients with non-resectable LARC – only in patients with resectable disease. However, based upon favourable treatment results in phase II trials, preoperative RCT has been regarded as "standard" therapy [2].

There is no uniform definition of LARC and to distinguish between a true LARC (with tumour infiltrating non-(readily)-resectable organs) and large non-fixed tumours need a great deal of clinical experience. In many preoperative trials no clear distinction between the stages has been made, and the term LARC has been used for T3-T4 resectable RC and even sometimes for lower stages.

The present study presents high dose RT and concurrent chemotherapy to patients with truly non-resectable RC. Acute toxicity was very low and only four patients experienced grade 3 toxicity and had a dose reduction of UFT. All but three patients received the planned 60 Gy dose without any delay (median treatment duration was 42 days). None of the patients had serious perioperative complications within 30 days. This combination treatment not only produces pCR but it also allows surgery and thus a chance of cure in more than 60% of the patients. Moreover the survival is very encouraging.

During the past decade the treatment strategy has been changed on several points. RT is given with five fields and the total radiation dose is increased. We have added oral chemotherapy and postponed the operation until at least 6 weeks after completing the RCT to allow maximum down-staging before surgery [15]. Before the present treatment strategy were introduced patients with LARC were treated with RT alone and they were evaluated for resection during or short after completion of RT. Compared to 29 consecutive historical controls the new treatment strategy (survival data from our phase I study) increased number of patients with R0 resection and prolonged survival [10,16]. The two patient populations may not be comparable but the results are encouraging.

Future challenges in RC are to improve the survival by an earlier diagnosis and by improving the combined oncological and surgical treatment. Based on the evidence that higher radiation doses improve tumour response and local control in other cancers [17], radiation dose escalation has been evaluated in rectal cancer. However, even with an optimal technique using conformal intensity-modulated radiotherapy, dose escalation in the pelvis is limited by rectal tolerance. Brachytherapy boost is an attractive way to deliver a high dose in a very small volume in rectal cancer. In the Lyon R96-02 randomised study more patients obtained a clinical complete response (29 vs. 2%) and more patients had sphincter preservation but unfortunately there

was no difference in morbidity, local recurrence rate or two-year overall survival [18].

In a Danish phase II study the total dose was increased to 65 Gy to the tumour bed with endorectal brachytherapy of 5 Gy/1 fraction in large T3 rectal cancers resulting in promising 27% pCR [19] but phase III trials are needed to define the possible role of brachytherapy as treatment option.

Optimizing the concurrent chemotherapy is a crucial question both in regarding chemotherapy as a radiosensitizer and as a treatment of subclinical metastases. In several studies, 5-FU has been the drug of choice with oral formulations as the most convenient for the patients. To our knowledge, UFT and capecitabine have never been compared head-to-head in a randomized study, neither as chemotherapy nor as a radiosensitizer. However the Mayo regimen (5 days of bolus 5-FU/leucovorin every 28 days) has been compared with UFT and capecitabine separately in patients with disseminated colorectal cancer, indirectly indicating comparable efficacy at least in terms of survival [20,21].

Oxaliplatin and irinotecan are excellent radiosensitizers often used in combination with 5-FU infusions or the oral formulations. Hartley et al. [9] collected data from several studies with more than 3 000 patients and on multivariate analysis they found that the use of a second drug (often oxaliplatin or irinotecan) was associated with higher rates of pCR (may be a surrogate marker for efficacy). When combined with 5-FU or 5-FU prodrugs, both drugs appear to have comparable toxicities and efficacies and the available data do not suggest any specific advantage of oxaliplatin or irinotecan [22]. Efficacy of RCT may be improved even further by adding the new biological agents (e.g., cetuximab or bevacizumab) but these combinations must be investigated in large randomized trials.

Whether neoadjuvant chemotherapy (NACT) before RCT should be a treatment option have also been questioned. This could be an advantage in terms of eradicating distant metastases at an early stage of the disease, reducing the primary tumour volume and consequently reduce the high-dose radiation volume, and tumour shrinkage potentially allows improved tumour vascularity. Disadvantages are that chemotherapy will delay the definitive local treatment, that chemotherapy favours the selection of radio-resistant clones and may reduce the efficacy of subsequent RT. However, the data in favour of NACT before RCT is inconclusive, should be used with caution, and only in clinical trials [23].

With the optimized RCT obtaining higher pathological complete response rates, the question of need for surgery in this subgroup of patients has been raised. Recently a Brazilian study compared the results after an operative versus a non-operative approach in patients with pCR, and this seems feasible [24]. This opens the question whether patients with T2-T3 resectable RC can be down-staged to T1-T2 with subsequent transanal endoscopic microresection (TEM) resulting in decreased morbidity in this group of patients. Whether a short-course RT can result in down-staging the tumour with delayed resection is now being investigated in a Swedish randomized phase III trial in which patients with resectable RC are randomized to RT with 25 Gy/5 fx immediately followed by TME, 25 Gy/5 fx and TME after 4 weeks or 50 Gy/25 fx and TME after 4 weeks [25].

Until now there has been conducted several phase II studies combining RT and chemotherapy preoperatively in "locally advanced" RC and because of the often not clear distinction between the stages of the patients entering these studies, it is virtually impossible to draw conclusive data from non-randomized comparisons of these studies. Randomized phase III trials are now warranted.

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