Palliative radiotherapy and chemotherapy instead of surgery in symptomatic rectal cancer with synchronous unresectable metastases: a phase II study†

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Background: In stage IV rectal cancer, palliative surgery is often carried out upfront. This study investigated whether the surgery can be avoided.

Patients and methods: Forty patients with symptomatic primary rectal adenocarcinoma and synchronous distant metastases deemed to be unresectable received 5 × 5 Gy irradiation and then oxaliplatin-based chemotherapy. Before treatment, 38% of patients had a near-obstructing lesion. The palliative effect was evaluated by questionnaires completed by the patients.

Results: The median follow-up for living patients was 26 months (range 19–34). The median overall survival was 11.5 months. Eighty patients (20%) required surgery during the course of their disease: seven patients required stoma creation and one had local excision. Thirty percent of patients had a complete resolution of pelvic symptoms during the whole course of the disease, and 35% had significant improvement. In the subgroup with a near-obstructing lesion, 23% of patients required stoma creation. In all patients, the probability of requiring palliative surgery at 2 years was 17.5% [95% confidence interval (CI) 13% to 22%], and the probability of sustained good palliative effect after radiotherapy and

References:

Introduction

Synchronous distant metastases are diagnosed in \sim 20\% of patients with rectal cancer, most of whom are treated with palliative intent [1]. Creation of a diverting stoma or palliative primary tumour resection is often carried out before chemotherapy is started [1]. The main objectives of such treatment are to achieve fast relief from pelvic tumour-related symptoms and to avoid complete bowel obstruction or perforation necessitating emergency surgery in the future. The issue of whether primary tumour resection leads to survival benefit is a matter of controversy [1]. A stoma impairs some aspects of quality of life, and primary tumour resection has become controversial because of the increased efficacy of systemic treatment [1]. In addition, surgery creates a risk of delaying or not receiving chemotherapy if there is a surgical morbidty.

We hypothesized that the palliative effect of radiotherapy and chemotherapy is sufficient to spare patients from surgery during the course of their disease. Short-course radiotherapy (5 \times 5 Gy) followed by oxaliplatin-based chemotherapy given in tight sequence may be considered. With this treatment, chemotherapy can be delivered in full doses, whereas, if combined simultaneously with irradiation, the chemotherapy doses must be reduced. In the preoperative setting, such management yielded a complete pathological response in 21\%–26\% of patients [2, 3]. A randomized trial comparing this treatment with conventionally fractionated chemoradiation in the preoperative setting showed similar local effectiveness, as measured by the pathological response, in two arms [3]. For the above reasons, we chose short-course irradiation as the initial management. The aim of our trial was to determine the safety of this treatment in patients with symptoms related to the primary tumour.

Methods

The primary end point of the trial was the rate of surgery carried out for palliation of local symptoms that were uncontrolled by upfront short-course radiotherapy and chemotherapy. The secondary end points were the palliative effect, acute radiation toxicity and tumour-related prognostic factors as predictors of poor palliative effect.

The study was approved by the ethics committee. The eligibility criteria included previously untreated symptomatic primary rectal adenocarcinoma proven by pathological examination, synchronous distant metastases deemed to be never resectable, lower border of the tumour located up to 10 cm from the anal verge and signed informed written consent. The exclusion criteria were an asymptomatic primary tumour, complete bowel obstruction, metastatic disease judged as potentially resectable after chemotherapy and a previously created stoma. Based on the computed tomography (CT) image, decisions about the unresectability of distant metastases were made by colorectal surgeons at multidisciplinary meetings. Stent placement was not considered because in patients with low-lying rectal cancer, it may result in intractable anal pain, tenesmus and incontinence [4]. All patients who met the entry criteria were registered prospectively.

Treatment

The irradiated planned target volume included the primary tumour and adjacent enlarged lymph nodes plus a 1 cm margin. Uninvolved regional nodes and enlarged nodes located some distance from the primary were not irradiated. Three-dimensional planning was used. The dose was specified at the intersection of the axes of the fields. Patients with a distended urinary bladder were irradiated on a belly-board device using 15 MV photon beams. Five fractions of 5 Gy were given over five consecutive days. We decided to deliver chemotherapy as soon as possible after radiotherapy to enhance the effect of radiation. Because some patients may experience acute toxicity a few days after delivery of 5 \times 5 Gy [3], chemotherapy was postponed until 9 days after radiation to avoid overlapping toxicity. Radiation was given Monday through to Friday, and chemotherapy was started on Monday after a 1-week rest. In cases of persistent acute radiation toxicity, chemotherapy was delayed until recovery. The protocol stipulated CAPOX (oxaliplatin given intravenously at 130 mg/m² on day 1, followed by oral capecitabine 1000 mg/m² twice daily on days 1–14, in a 3-week cycle). Chemotherapy was carried out until progression or unacceptable toxicity. Treatment interruption in cases of disease stabilization was allowed. Second and consecutive lines of chemotherapy or targeting treatment were used at the discretion of the treating oncologist.

Follow-up

Patients were informed that, in cases of a poor palliative effect, surgical intervention is preferable to watchful waiting to avoid the need for an emergency operation. At the follow-up visits, this problem was discussed with the symptomatic patients and surgical opinion about the need of intervention was requested. Evaluation of response of the primary tumour on CT or MRI was not required because its regression after radiotherapy may take several months and a non-progressive asymptomatic lesion may persist for a few years [5]. Acute toxicity occurring during radiotherapy was scored by a physician using the NCI CTC v. 3 scale. The evaluation of the palliative effect was based on each patient’s opinion expressed in non-validated self-administered questionnaires (S1) 1 month after radiotherapy and every 3 months thereafter. Patients reported on the most severe symptom before radiotherapy, acute radiation toxicity after irradiation, responses of symptoms to radiation and any new symptoms that may have occurred. Patients were also asked to express their opinion as to whether, in their case, upfront radiotherapy was a suitable management tool or whether initial surgery would have been a better solution.

Statistics

Using the study hypothesis that after radiotherapy and chemotherapy at least 30\% (95\% confidence interval (CI) 10\% to 50\%) of patients can avoid surgery, a sample size of 20 patients was calculated. The ethics committee agreed to increase the sample size to 40 patients after observations showing favourable preliminary results. Tumour characteristics were evaluated using...
clinical information and CT carried out for radiotherapy planning. CT examinations were evaluated independently by two investigators, one a radiation oncologist (DT-S) and the other a radiologist (JP), using a report form. Discrepancies were resolved by consensus. The cumulative incidence of carried out palliative surgery was calculated using competitive risk analysis. The competing events were palliative surgery (event of interest), death or attempted radical surgery of the primary tumour, whichever occurred first. Patients alive without having palliative surgery were censored at the last observation. The palliative effect was evaluated by calculating the probability of sustained good palliative effect using competitive risk analysis and the following formula: 1 – the cumulative incidence of poor palliative effect. Good palliative effect was defined as a complete resolution of the initial primary tumour-related symptoms or significant reduction in their intensity and no occurrence of new local symptom(s) of significant intensity. Poor palliative effect was defined as a slight or no response of symptoms, or reappearance, progression of symptoms during the course of the disease in patients with initially good palliation or occurrence of new local symptom(s) of significant intensity. Competing events were poor palliative effect (event of interest), death or attempted radical surgery of the primary tumour, whichever occurred first. The Kaplan–Meier method was used to estimate survival. All time intervals were measured from the first day of radiotherapy. The chi-square test or Fisher’s exact test was used to compare proportions. All tests were two-sided. The data were analysed with SPSS software version 19 for Windows (SPSS, Inc., Chicago, IL) and R software http://cran.r-project.org/ accessed December 2012.

results

Between September 2009 and February 2011, participation in the trial was offered to all 42 patients referred to our tertiary referral centre who met the entry criteria. All agreed to participate. At that time, all unresectable stage IV patients referred to our centre had pelvic symptoms. Two patients were excluded, leaving 40 patients for the analysis. In one of the excluded patients, a second pathology opinion showed squamous cell carcinoma; in the other one, the surgeon and the patient had decided arbitrarily to create a stoma 1 week after radiotherapy without any progression of symptoms. The patients’ characteristics are shown in Tables 1 and 2. A near-obstructing lesion (it was impossible to advance the colonoscope beyond the tumour) was reported in 38% of patients. Thirty-nine patients (97.5%) received 5 × 5 Gy, and the other patient received 30 Gy in six fractions. Toxicity was reported to occur more often a few days after irradiation than during irradiation: 65% versus 17.5% (S2). In five patients (12.5%), chemotherapy was delayed for a few days until acute symptoms resolved. None of the patients required hospitalization because of radiation toxicity.

Chemotherapy was given to 37 patients (92.5%): 23 received CAPOX, 7 received other oxaliplatin-based schedules and 7 frail patients received capecitabine alone. The three remaining patients (7.5%) did not receive chemotherapy because of their poor performance status. Chemotherapy was started 4–19 days (median 9) after completion of radiotherapy. Seven patients received chemotherapy earlier than required by the protocol. Possibly for this reason, severe toxicity occurred shortly after chemotherapy in three of these seven patients; one patient was hospitalized because of prolonged diarrhoea.

None of the patients were lost to follow-up. Twenty-nine patients (72.5%) died. The follow-up period for the 11 surviving patients was 19–34 months (median 26). The median overall survival was 11.5 months (95% CI 8.0–15.1). Overall survival at 2 years was 30% (95% CI 15% to 45%).

surgery

Eight patients (20%) had palliative surgery because of local symptom progression. None of these operations were emergent. Seven patients required creation of a stoma: five because of obstructive symptoms and two because of a perianal fistula. The eighth patient required a full-thickness local excision because of bleeding. One patient died within 30 days after surgery. In none of the three patients receiving only radiation surgery was needed. Seven surgical procedures were carried out within 12 months of radiotherapy, and the eighth after 34 months. Eight of the 11 surviving patients (73%) did not require palliative surgery. Of the 29 patients who died, 24 (83%) did not require palliative surgery. The probability of palliative surgery at 2 years was 17.5% (95% CI 13% to 22%) (Figure 1).

After obtaining a second opinion, in four patients radical surgery of both the primary tumour and distant metastases was attempted 4–10 months after radiotherapy. All of these patients had a good palliative effect before surgery. In three of these
patients, the primary tumour was resected, and in the fourth only a stoma was created.

**Responses of symptoms to treatment**

Response rates to the questionnaires 1 month, 3 months, 1 year and 2 years after treatment were 100%, 92%, 100% and 100%, respectively. Such high rates were achieved because 65 of 188 questionnaires (35%) were completed by telephone when not received on time.

Within 1 month of completing radiotherapy, 8 patients (20%) reported complete resolution of the most severe pelvic tumour-related symptom, 17 (42.5%) reported significant improvement, 11 (27.5%) slight improvement and 4 (10%) reported no change in symptom. None of the patients reported worsening of the symptom. During further follow-up, the intensity of pelvic symptoms diminished in 18 patients.

To analyse the global palliative effect in each patient, the score showing the worst result was chosen from the questionnaire completed 3 months post irradiation and later. Twelve patients (30%) reported complete symptom resolution and 14 (35%) reported significant resolution during the whole course of the follow-up. Fourteen patients (35%) had a poor palliative effect, eight of whom had palliative surgery. Of the six other patients, one died because of massive haemorrhage of the primary tumour. The deaths of another two patients were preceded by severe pelvic tumour-related symptoms: one had bleeding from the primary tumour requiring blood transfusion and the other had severe bowel obstructive symptoms. Palliative surgery was not carried out in these two patients because of their poor performance status. One of the six patients experienced bleeding from the primary tumour and received a second course of radiotherapy with a favourable effect. The two remaining patients had a poor symptom response but did not consent to palliative surgery. The 14 patients with a poor palliative effect reported progression of the initial symptoms, and four of them also reported additional new local symptoms. The probability of a sustained good palliative effect at 2 years was 67% (95% CI 58% to 76%) (Figure 2). Apart from one death because of massive haemorrhage mentioned above, no other deaths could be directly attributed to the acute complications of the primary tumour such as bowel perforation, or obstruction. None of the patients with a poor palliative effect had stent placement or laser ablation.

None of the tumour-related variables showed a significant association with a poor palliative effect (Table 2). A poor palliative effect was observed in 38% of patients with a near-obstructing lesion compared with 33% of patients with a wider lumen of the bowel wall. Of note, 23% of patients with a near-obstructing lesion required stoma creation.

Of the 30 patients who answered the question about their preference, 26 (87%) claimed that the upfront radiotherapy provided better management than upfront surgery would have; the four other patients (13%) claimed that the upfront surgery would have been a better treatment.

### Table 2. Associations between tumour characteristics and palliative effects

<table>
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<tr>
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<th>Poor palliative effect, N = 14 (%)</th>
<th>Good palliative effect, N = 26 (%)</th>
<th>P-value</th>
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<tr>
<td>Intensity of pelvic symptoms</td>
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<td>Mild</td>
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<td>Severe</td>
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<td>12 (55)</td>
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<td>Near-obstructing tumour</td>
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<td>5 (38)</td>
<td>8 (62)</td>
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<tr>
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</table>

For continuous variables, the median value was used as the cut-off point.

* A good palliative effect was defined as complete resolution of primary tumour-related symptoms or significant reduction in their intensity after radio- and chemotherapy lasting throughout the whole observation period with no occurrence of new local symptom(s).

bNear-obstructing tumour was diagnosed when it was impossible to advance the colonoscope beyond the primary tumour.

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**Figure 1.** Cumulative incidence of palliative surgery. Competitive risk analysis of events: palliative surgery (event of interest), death, or attempted radical surgery of the primary tumour, whichever occurred first.
prospective study, laser ablation was combined with palliative radiotherapy was used instead of surgery [6]. Only three series were found in which palliative therapy was applied. Only three series were found in which palliative treatment was applied. These results, however, need to be interpreted with caution because some patients scored the palliative effect as more favourable than did their family (data not shown).

We searched PubMed using the terms 'rectal cancer', or 'rectal adenocarcinoma', and 'palliative radiotherapy', or 'neoadjuvant chemotherapy'. No date or language restrictions were applied. Only three series were found in which palliative radiotherapy was used instead of surgery [6–8]. In one prospective study, laser ablation was combined with palliative radiotherapy. Two other series were retrospective. Similar findings to those observed in the current investigation were reported. This is in line with high effectiveness of $5 \times 5$ Gy and consolidation chemotherapy shown in the neoadjuvant setting [2, 3].

A weakness of our trial is the lack of a control group treated with initial palliative surgery or a control group treated with chemotherapy alone. In the latter strategy, palliative radiotherapy or palliative surgery could be reserved only for patients for whom chemotherapy fails to control local symptoms. This could spare many patients from the acute toxic effects of radiotherapy. In addition, it is possible that haematological tolerance to chemotherapy and its dose intensity would have been better because pelvic bone marrow was not damaged by irradiation.

The use of chemotherapy alone as an initial treatment was suggested by a recent phase II study of stage IV colon cancer patients [9]. Only 12% of those patients required surgery for an uncontrolled primary tumour during the course of the disease. The long-term effect of upfront chemotherapy alone is also known from a retrospective study of 233 patients with stage IV colorectal cancer [10]. Only 11% of those patients required surgery for primary tumour complications during the course of the follow-up. The risk of surgery was not associated with tumour location (rectum versus colon). However, in those two studies, only patients with an asymptomatic primary tumour were included and most patients had colon cancer. In contrast, all patients in our study had primary tumour-related symptoms. Two studies reported by Chau et al. [11, 12] prospectively evaluated the symptom response of primary rectal cancer to chemotherapy alone in the neoadjuvant setting. In one study, 65% of patients had improvement or resolution of symptoms; in the other study, 86% of patients had complete resolution. In both the studies, improvement was observed after 1 month, i.e. just over one cycle. These figures contrast with the 20% of patients in the present series who had a complete resolution of symptoms after radiotherapy and one course of chemotherapy. It is unknown whether the aforementioned merits of using chemotherapy alone, compared with the combination with radiotherapy, would outweigh the potential disadvantage of weaker and shorter relief from symptoms. A randomized trial comparing chemotherapy alone with chemoradiation added to chemotherapy in the postoperative setting showed improved local control in the chemoradiation group [13].

Another weakness of our study is the lack of use of laser ablation. This likely would have further diminished the need for stoma creation [4]. However, laser ablation is relatively ineffective in patients with a long-segment or circumferential tumour or with an angulated segment of the rectum [4].

The strength of our study is the lack of selection bias within our institution because all patients who were referred to our centre and who met the entry criteria participated in the study. This supports the generalizability of our results.

In conclusion, initial short-course palliative radiotherapy and chemotherapy allowed most patients to avoid surgery, even those with a near-obstructing tumour. These findings suggest that short-course radiotherapy is a valid option and can replace upfront palliative surgery.

Figure 2. The probability of a sustained good palliative effect. A good palliative effect was defined as complete resolution of primary tumour-related symptoms or significant reduction in their intensity after radio- and chemotherapy lasting throughout the whole follow-up period with no occurrence of new local symptom(s). Competitive risk analysis of events: poor palliative effect (event of interest), death or attempted radical surgery of the primary tumour, whichever occurred first.

discussion

This study shows that the need for initial surgery may be avoided in a high proportion of patients by using palliative radiotherapy and chemotherapy. Once achieved, the palliative effect was most often long-lasting (Figures 1 and 2). A rescue surgery was carried out in most patients with a poor palliative effect. In three patients (7.5%), the lack of upfront surgery possibly led to death because of massive haemorrhage or to suffering that preceded death. Acute radiation toxicity was usually mild and of short duration (S2). This low toxicity can be explained by using a small irradiation target volume and conformal technique. Our results suggest that chemotherapy should not be commenced earlier than 1 week after irradiation; otherwise, toxicity of the two treatments may overlap. We were unable to identify tumour features that could predict the failure of radiotherapy and chemotherapy to palliate (Table 2). Even patients with signs of a near-obstructing tumour had a reasonable chance of avoiding surgery. Evaluation of patients’ preferences showed that most opted for the upfront radiotherapy instead of upfront surgery. These results, however, should be interpreted with caution because some patients scored the palliative effect as more favourable than did their family (data not shown).

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In conclusion, initial short-course palliative radiotherapy and chemotherapy allowed most patients to avoid surgery, even those with a near-obstructing tumour. These findings suggest that short-course radiotherapy is a valid option and can replace upfront palliative surgery.
Unexpected toxicity of cetuximab combined with conventional chemoradiotherapy in patients with locally advanced anal cancer: results of the UNICANCER ACCORD 16 phase II trial†


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Background: The ACCORD 16 phase II trial aimed to evaluate the objective response rate after combination of conventional chemoradiotherapy (CRT) and cetuximab in locally advanced anal canal carcinoma (LAACC).

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REFERENCES