Phase II trial

A pilot study of accelerated preoperative hyperfractionated pelvic irradiation with or without low-dose preoperative prophylactic liver irradiation in patients with locally advanced rectal cancer

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Abstract

Background and purpose: To evaluate the feasibility of low-dose preoperative prophylactic liver irradiation (PLI) combined with preoperative accelerated hyperfractionated pelvic irradiation (HART) in patients with locally advanced rectal cancer.

Patients and methods: Between 1999 and 2003 62 patients were enrolled: 38 (61%) received HART and 24 (39%) HART + PLI. The pelvis was irradiated twice a day, with a minimal interfraction interval of 6 h: the total dose of 42 Gy was given in 1.5 Gy per fractions over 18 days. The PLI (14 Gy in 10 daily fractions of 1.4 Gy) was given simultaneously with the morning fraction of HART. Twenty patients (32%), including 7 in PLI group, received 5-Fu based postoperative chemotherapy.

Results: In general, acute normal tissue reactions appeared tolerable irrespectively of PLI. Six to twelve months after completion of combined therapy the mean ALAT levels in patients treated with HART alone (25 pts), HART + chemotherapy (13 pts), HART + PLI (17 pts), and HART + PLI + chemotherapy (7 pts) were 15, 21, 26 and 55 IU/l, respectively. A mild increase of ALAT levels observed in the HART + PLI + chemotherapy sub-group was non-symptomatic. Three-year actuarial loco-regional control rate in a group of 62 patients was 94%. None of the patients who received PLI developed metastases during the follow-up, compared to 10 out of 38 patients (26%) with no PLI. A difference in metastases-free survival in favor of HART + PLI can be, however, attributed to selection of patients for PLI who were in better general health and stage of disease than those treated with HART.

Conclusions: Further use of PLI may be limited due to asymptomatic, but detectable biochemical changes of liver function when PLI is sequentially combined with chemotherapy. HART, on the other hand, provides acceptable rate of local control, and is well tolerated, also when combined with postoperative chemotherapy.

Keywords: Rectal cancer; Preoperative radiotherapy; Hyperfractionation; Prophylactic liver irradiation

Selection of an optimal perioperative treatment for patients with locally advanced rectal cancer remains open to debate. In Scandinavian centers, a hypofractionated preoperative radiotherapy has been evaluated in randomized trials [5,20]. Some centers prefer simultaneous application of conventionally fractionated preoperative radiotherapy with 5-Fu based chemotherapy [17], while the other combine preoperative radiotherapy with brachytherapy [11]. Also, there are attempts to improve the therapeutic index by applying preoperative radiotherapy in short overall treatment time and low doses per fraction given 2–3 times a day [1,6,7,12,15,23,24]. The biological rationale for preoperative hyperfractionated accelerated radiotherapy (HART) is repopulation of tumor cells that may happen during fractionated radiotherapy [19], and improved sparing of late reacting normal tissues with small doses per fraction [21]. For preoperative pelvic irradiation a scheme proposed by Coucke et al. [6,7] has been adopted in the present study.

A similar debate continues over systemic treatment for rectal cancer [2]. Notably, distant metastases are the most common source of treatment failure, and liver is the most frequent site of distant spread. The data from a randomized trial [10] suggest that crude reduction in metastases rate from 5-fluorouracil based adjuvant chemotherapy in high-risk rectal cancer is about 7% (34 vs. 27%), which corresponds to the relative reduction of 20%. While other trials points that postoperative prophylactic liver irradiation does not offer much benefit in therapy for colorectal cancer [3,22], several theoretical premises exist to postulate that
prophylactic liver irradiation may become effective when introduced prior to surgery [18,26].

The primary aim of this study was to evaluate the feasibility of low-dose preoperative prophylactic liver irradiation (PLI) given for patients with locally advanced rectal cancer. The secondary aim was to assess the effect of HART when combined with postoperative chemotherapy, PLI or both.

Material/methods

Between July 1999 and July 2003 62 patients were enrolled to the phase I/II prospective clinical trial. Following selection criteria for hyperfractionated preoperative pelvic radiotherapy (HART) were observed:

(a) biopsy-proven adenocarcinoma of the rectum
(b) preoperatively assessed stage T3-4, or node-positive (N +): digital examination, proctosigmoidoscopy, transrectal ultrasound, CT and/or NMR of the pelvis in all of the patients
(c) operable tumor (fixed tumors were excluded)
(d) ZUBROD performace status 0–2
(e) age 20–80 years
(f) no prior radiation treatment
(g) no distant metastases (abdominal ultrasound, X-ray chest examination, other examinations if necessary)
(h) written consent for participation in the study

Twenty four (39%) out of 62 patients complied with the following additional criteria for the preoperative low-dose prophylactic liver irradiation:

(a) no history of liver diseases (viral hepatitis, cirrhosis, alcoholism)
(b) normal results of biochemical liver tests (alcalic phosphatase, ASPAT, ALAT)
(c) normal results of coagulation and bleeding tests (prothrombin time, caolin-kefalin time)
(d) patient’s age below 70 years
(e) written consent for liver irradiation

All of the patients considered eligible for the study were examined prior to therapy by a multidisciplinary team, which included surgeon, radiation oncologist, medical oncologist and anesthesiologist. The protocol of a trial was approved by the ethical committees related to the institutions in which it was performed.

Treatment schedule

All 62 patients received accelerated hyperfractionated irradiation (HART) to the pelvis. The total dose of 42 Gy was given in 28 fractions within 18 days (two fractions of 1.5 Gy per day, 10 fractions per week). A minimal interval between the fractions was 6 h. A subgroup of 24 patients selected for PLI received 14 Gy in 10 fractions to the whole liver, simultaneously with the morning fraction of HART.

Surgery (total mesorectal resection) was performed 2–18 days after radiotherapy (median 6 days).

The application of adjuvant postoperative chemotherapy with bolus 5-FU (425 mg/m² for 5 consecutive days) and leucovorin (20 mg/m² for 5 consecutive days) every 4 weeks for six courses was considered individually. Initially, it was given only to the patients with pathologically proven metastases to the lymph nodes who did not receive PLI. Thereafter, it was also given to node-positive patients who underwent PLI. Overall, chemotherapy was given to 20 patients (32%), seven of them received PLI.

Radiation treatment technique

Three-field (one posterior and two lateral fields) isocentric technique was used to irradiate the pelvis. Patients were placed in a prone position and immobilized in a thermoplastic mask. An individual 3D treatment planning was used. Portal vision and in vivo dosimetry was used to control the referral points and the dosimetric parameters. Photons of energy 6–23 MV were used.

The irradiated volume included primary tumor with at least 3 cm margin, internal iliac and presacral nodes. The lumbo-sacral plexus was shielded. Liver was irradiated from two opposite fields, which were angled to exclude the right kidney; 3D planning and conformal conditions (MLC) were applied.

Evaluation of acute and late normal tissue reactions

Acute normal tissue reactions were evaluated twice a week during radiotherapy using a Dische scale [8]. The total severity score represented sum of scores attributable to particular reactions: erythema, tenesmus, diarrhea, nausea, pain, rectal bleeding, ulceration, pollakiuria. The maximum possible score was 36. The incidence of fistulas, ileus, and lumbar plexus neuralgia was also scored.

All of the patients had repeated measurements of ASPAT, ALAT, alcalic phosphatase, prothrombin and caolin-kefalin time at first and last week of radiation treatment, as well as 6, 12, 24 and 36 months after the therapy. In patients who underwent the abdomino-perineal resection the duration of perineal wound healing was measured.

Characteristics of the patients

Between 1999 and 2003, 62 patients have been enrolled: 38 received HART and 24 HART + PLI (Table 1). Liver irradiation was withheld more often than expected at the study design, most often due to lack of patients consent for the novel therapy, late age of patients, abnormal results of liver and/or coagulation tests, and/or history of liver diseases.

Median age in a whole group (38 men and 24 women) was 60 years (range from 38 to 77). Median age in PLI and HART with no PLI sub-groups was 56 vs. 64 years, respectively.

The pretreatment clinical and pathological stage has been evaluated according to the sixth edition of the AJCC TNM system. A difference in a proportion of the patients within specific TN stage before and after treatment (Table 1) may reflect tumor response to preoperative radiation therapy: in only one in 62 patients (1.6%) the primary tumor did not appear to penetrate through muscularis propria at pretreatment ultrasound (cT2), compared to 17/62 tumors (27.4%) pathologically classified as ypT2. By contrast, the number of node-positive cases has increased from 12/62 (19.3%) atpretreatment evaluation to 21/62 (33.9%) at pathological staging. This, likely, reflects detection of subclinical metastases to lymph nodes at pathological
evaluation. Distant metastases were found in three patients at the time of surgery: two of them treated with HART and in one treated with PLI.

Median follow-up time was 2.9 years for HART (range 0.3–5.1 years) vs. 2.7 years for HART + PLI (range 0.8–5.2 years). One patient in HART was lost to follow-up 0.3 years after treatment.

Statistical methods

The average maximum total Dische severity score in HART + PLI sub-group was 5.3 (range 1–12) vs. 4.8 (range 0–12) in patients who did not undergo PLI ($P = 0.69$). While lack of statistical difference in total Dische score may suggest that the therapy was equally well tolerated regardless of PLI, a noticeable difference was observed with respect to nausea. Two patients from PLI sub-group required a gap due to grade 3 nausea, compared to one patient who did not receive PLI (nausea, however, was associated with a disease-related mechanical ileus in this patient). Tenesmus and diarrhea, while frequent in both groups, were mild and well-controlled by the supportive pharmacological management.

In both sub-groups, a mild asymptomatic leukopenia was recorded at the end of radiation treatment: the mean white blood cell count was 4600 vs. 4200/ml for HART and HART + PLI, respectively. In none of the patients, however, WBC dropped below 2000/ml.

In general, the biochemical tests performed at various intervals after the therapy have shown a mild increase of ALAT levels compared to pretreatment findings. In HART group the mean ALAT level (IU/l) measured before and at the end of radiation therapy was 15 vs. 25, compared to 23 vs. 34 in HART + PLI group. Six to twelve months after completion of combined therapy the mean ALAT levels (IU/l) in patients treated with HART alone (25 pts), HART + chemotherapy (13 pts), HART + PLI (17 pts), and HART + PLI + chemotherapy (7 pts) were 15, 21, 26 and 55 IU/l, respectively. While ALAT levels evaluated during the follow-up in seven patients who received HART + PLI + chemotherapy appeared to be significantly higher than in the remainders ($P = 0.01$) the degree of long-term biochemical damage to the liver can be considered mild, given that the upper normal ALAT level is 40 IU/l. Most importantly, none of the patient presented clinical symptoms, which could be related to hepatic injury.

The administration of HART + PLI or HART + PLI + chemotherapy did not significantly influence the levels of ASPAT, prothrombin or caolin-kefalin time, neither during therapy, therapy did not significantly influence the levels of ASPAT, prothrombin or caolin-kefalin time, neither during therapy, nor at the follow-up. A prolonged perineal wound healing (> 2 months) was observed in 11 (50%) of 22 patients who underwent abdomino-perineal amputation, with longest healing time of 6 months. No other serious adverse effects of surgery radiotherapy or chemotherapy were observed.

### Results

#### Treatment compliance

Radiation therapy was completed according to the protocol in 59 patients: one patient who did not undergo PLI developed ileus, two patients treated with HART + PLI had grade 3 nausea and, apart from anti-emetic drugs, required radiation treatment gap of one week.

Anterior resection was performed in 37 patients (59.7%), 22 patients (35.5%) underwent abdomino-perineal resection; two patients (3.2%) had Hartmann’s surgery, one patients underwent laparotomy (multiple liver metastases were found at surgery).

All 20 patients appointed for postoperative chemotherapy received six courses of 5-Fu and leucovorin. In two patients treated with HART + PLI unplanned gaps in chemotherapy of 4–6 weeks were introduced because of fatigue reported by the patients and above-normal levels of ALAT.

#### Acute and late normal tissue reactions

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#### Table 1

Characteristics of 62 rectal cancer patients enrolled to the study on accelerated preoperative hyperfractionated pelvic radiotherapy (HART) with or without low-dose preoperative prophylactic liver irradiation

<table>
<thead>
<tr>
<th>Variable</th>
<th>HART N = 38</th>
<th>HART + PLI N = 44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&lt; 60)</td>
<td>17 (44.7%)</td>
<td>15 (62.5%)</td>
</tr>
<tr>
<td>Age (≥ 60)</td>
<td>21 (55.3%)</td>
<td>9 (37.5%)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>17 (44.7%)</td>
<td>7 (29.2%)</td>
</tr>
<tr>
<td>Male</td>
<td>21 (55.3%)</td>
<td>17 (70.8%)</td>
</tr>
<tr>
<td>yTN (clinical stage before radiotherapy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3N0</td>
<td>24 (63.1%)</td>
<td>19 (79.2%)</td>
</tr>
<tr>
<td>T2N +</td>
<td>1 (2.6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>T3N +</td>
<td>8 (21.0%)</td>
<td>3 (12.5%)</td>
</tr>
<tr>
<td>T4N0</td>
<td>5 (13.2%)</td>
<td>2 (8.3%)</td>
</tr>
<tr>
<td>pTN (postoperative pathological stage)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2N0</td>
<td>7 (18.4%)</td>
<td>6 (25.0%)</td>
</tr>
<tr>
<td>T3N0</td>
<td>17 (44.7%)</td>
<td>10 (41.7%)</td>
</tr>
<tr>
<td>T4N0</td>
<td>0 (0%)</td>
<td>1 (4.2%)</td>
</tr>
<tr>
<td>T2N1</td>
<td>3 (7.9%)</td>
<td>1 (4.2%)</td>
</tr>
<tr>
<td>T3N1</td>
<td>6 (15.8%)</td>
<td>4 (16.8%)</td>
</tr>
<tr>
<td>T4N1</td>
<td>0 (0%)</td>
<td>1 (4.2%)</td>
</tr>
<tr>
<td>T2N2</td>
<td>4 (10.5%)</td>
<td>1 (4.2%)</td>
</tr>
<tr>
<td>T4N2</td>
<td>1 (2.7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior resection</td>
<td>24 (63.2%)</td>
<td>13 (54.1%)</td>
</tr>
<tr>
<td>Abdomino-perineal resection</td>
<td>12 (31.5%)</td>
<td>10 (41.7%)</td>
</tr>
<tr>
<td>Explorative laparotomy</td>
<td>0 (0%)</td>
<td>1 (4.2%)</td>
</tr>
<tr>
<td>Hartmann’s resection</td>
<td>2 (5.3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13 (34.2%)</td>
<td>7 (29.2%)</td>
</tr>
<tr>
<td>No</td>
<td>25 (65.8%)</td>
<td>17 (70.8%)</td>
</tr>
</tbody>
</table>
Local control, distant metastases, and overall survival

Local recurrence has been detected in 4 out of 62 patients (6%), two of them treated with PLI. The actuarial 3-year loco-regional recurrence-free survival in a whole group of 62 patients was 94% (Fig. 1).

Ten out of 38 patients (26%) treated with HART developed distant metastases, including five with liver metastases, three with lung metastases, and two with metastases at the other sites. In a subgroup of 13 patients at high risk of dissemination who received HART + chemotherapy, five individuals (38%) developed distant metastases. By contrast, out of 24 patients who received PLI none of the patients developed metastases during the follow-up, whereas in one patient they were detected at the time of surgery. The actuarial 3-year metastases-free survival was 71 vs. 96% for HART and HART + PLI, respectively (Fig. 2). A 3-year actuarial overall survival rate was 65 and 92% for HART and HART + PLI groups, respectively. Overall, 13 out of 62 patients died, including 11 who died of cancer, and two of cardiac diseases.

Discussion

Local effectiveness and tolerance of accelerated hyperfractionated preoperative radiotherapy

A progressively widespread use of total mesorectal resection and preoperative adjuvant radiotherapy contributed for improvement in cure rates for rectal cancer over the last years [16]. A 6% rate of loco-regional recurrences at 3 years reported in the present study is comparable to that reported in the recent literature [7,14]. Accelerated hyperfractionated preoperative radiotherapy of the pelvis was well tolerated, and only prolonged wound healing in patients after abdomino-perineal resection was of clinical concern. We did not observe any of the adverse effects, which were reported in older trials on hypofractionation, which employed obsolete treatment techniques [9,13].

An apparent downstaging has been observed in approximately 30% of the patients, which is, likely, less than one would expect after preoperative radio-chemotherapy [4]. A proportion of the patients who underwent anterior resection (60%) is, nevertheless, higher than that reported in Swedish trial evaluating short hypofractionation [20], and comparable to those recently reported by the Dutch and Warsaw groups [4,14]. In our opinion, accelerated hyperfractionated preoperative radiotherapy to the pelvis deserves attention in future research on adjuvant therapy for rectal cancer. A phase III trial designed to compare local effectiveness and tolerance of hyperfractionated and hypofractionated preoperative radiotherapy to the pelvis has recently opened accrual in Gliwice.

The present results support conclusions of Coucke et al. [7], that as a consequence of improvement in loco-regional cure rates for rectal cancer, distant metastases become the most frequent site of treatment failure. Metastases appeared in 18% of our patients, in spite that adjuvant chemotherapy has been used in 20 individuals considered to be at high risk of dissemination. This illustrates that the effectiveness of 5-Fu based postoperative chemotherapy is limited, and provides the background for search of new strategies, which would enhance or replace currently used treatment strategies.

Should prophylactic liver radiotherapy be used in the future?

The results of a randomized clinical trials on postoperative prophylactic liver irradiation in patients with adenocarcinoma of colon and rectum were disappointing [3,22] and it was postulated that prophylactic liver irradiation should be condemned. Considering, however, as a paradigm, the development of strategies for pelvic irradiation we have hypothesized that low radiation doses applied preoperatively to the liver may be more effective than those applied after the surgery. Such hypothesis is supported by the data, which show that low radiation doses may effectively sterilize subclinical cancer, if only applied without any considerable time delay relative to therapy for primary cancer [18,19,26]. Theoretically, the dose of 14 Gy may reduce the incidence of metastases within irradiated volume by approximately 20–30% [25,26] (Fig. 3), the effect being comparable to that of adjuvant chemotherapy. Such effect
may be, however, presumably enhanced when elective radiotherapy and chemotherapy are combined.

A high metastases-free survival rate among the patients who underwent PLI has been documented in the present study. The HART and HART + PLI groups were, however, not the same in terms of general health and stage of the disease. One should not, thus, attribute the difference in metastases-free survival between the groups exclusively to the effect of PLI. Clearly, a reliable evaluation of the effectiveness of PLI would require a randomized study.

More can be inferred about the tolerance of PLI: the present data show that acute and late toxicity of PLI without chemotherapy is acceptable. However, when PLI was sequentially combined with 5-Fu the subclinical, biochemically detectable changes of liver function were observed. While non-symptomatic changes in biochemical liver function may be considered acceptable if accompanied by significant reduction in metastases rate, an apparent limitation for evaluation of PLI in a randomized setting would be poor accrual of the patients for this therapy. Also, it appears that the observed profile of acute and late toxicity of PLI does not leave much field for treatment intensification, e.g. concurrent use of chemotherapy and PLI. While low-dose PLI with or without chemotherapy may deserve further attention we did not opt for a phase III trial on PLI for rectal cancer at our institution.

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