Radiotherapy and Oncology 106 (2013) 198–205

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Rectal cancer

Preoperative radiotherapy and local excision of rectal cancer with immediate radical re-operation for poor responders: A prospective multicentre study ☆

Krzysztof Bujko [a,*,1], Piotr Richter [b,1], Fraser M. Smith [c,1], Wojciech Polkowski [d,1], Marek Szczepkowski [e,1], Andrzej Rutkowski [a,1], Adam Dziki [f,1], Lucyna Pietrzak [a,1], Milena Kołodziejczyk [a,1], Jerzy Kuśnierz [a,1], Tomasz Gach [b,1], Jan Kulig [b,1], Grzegorz Nawrocki [a,1], Jakub Radziszewski [a,1], Ryszard Wierzbicki [d,1], Teresa Kowalska [g,1], Wiktor Meissner [h,1], Andrzej Radkowski [i,1], Krzysztof Paprota [j,1], Marcin Polkowski [k,1], Anna Rychter [l,1]

[a] Department of Radiotherapy, Maria Sklodowska-Curie Memorial Cancer Centre, Warsaw; [b] Department of Surgery, Jagiellonian Medical University College, Krakow, Poland; [c] Department of Colorectal Surgery, Cleveland Clinic, OH, USA; [d] Department of Surgical Oncology, Medical University, Lublin; [e] Department of Rehabilitation, Jozef Piłsudski University of Physical Education, Warsaw; [f] Department of Colorectal Surgery, Medical University, Lodz; [g] Department of Surgery, Maria Sklodowska-Curie Memorial Cancer Centre, Krakow; [h] Department of Surgery, Medical University, Poznan; [i] Department of Radiotherapy, Regional Cancer Centre, Tarnow; [j] Department of Radiotherapy, Regional Cancer Centre, Lublin, Poland; [k] Department of Gastroenterology and Hepatology, Medical Center for Postgraduate Education, Warsaw; and [l] Department of Radiotherapy, Regional Cancer Centre, Lodz, Poland

ARTICLE INFO

Article history:
Received 13 January 2012
Received in revised form 13 December 2012
Accepted 13 December 2012
Available online 17 January 2013

Keywords:
Rectal cancer
Preoperative radiotherapy
Local excision

ABSTRACT

Purpose: To assess local control after preoperative radiation and local excision and to determine an optimal radiotherapy regimen.
Methods: Eighty-nine patients with G1–2 rectal adenocarcinoma <3–4 cm; unfavourable cT1N0 (23.6%), cT2N0 (62.9%) or borderline cT2/cT3N0 (13.5%) received 5 × 5 Gy plus 4 Gy boost (71.9%) or 55.8 Gy in 31 fractions with 5-FU and leucovorin (28.1%). Local excision (traditional technique 56.2%, transanal endoscopic microsurgery 41.6%, Kraske procedure 2.2%) was performed 6–8 weeks later. If patients were downstaged to ypT0–1 without unfavourable factors (good responders), this was deemed definitive treatment. Immediate conversion to radical surgery was recommended for remaining patients.
Results: Good response to radiation was seen in 67.2% of patients in the short-course group and in 80.0% in the chemoradiation group, $p = 0.30$. Local recurrence at 2 years (median follow-up) in good responders was 11.8% in the short-course group and 6.2% in the chemoradiation group, $p = 0.53$. In the total group, a lower rate of local recurrence at 2 years was observed in elderly patients (>69 years, median value) when compared to the younger patients; 8.3% vs. 27.7%, Cox analysis hazard ratio 0.232, $p = 0.016$. A total of 18 patients initially managed with local excision required conversion to abdominal surgery but either refused it or were unfit. In this group, local recurrence at 2 years was 37.1%.
Conclusions: This study suggests an acceptable local recurrence rate after preoperative radiotherapy and local excision of small, radiosensitive tumours in elderly patients.
 Radiotherapy and Oncology 106 (2013) 198–205

In theory full-thickness local excision of rectal cancers is an attractive treatment yet its widespread implementation is limited due to reported increases in local recurrence as compared to radical surgery. Its advantages over abdominal surgery are that it both avoids the need for a stoma and has significantly reduced peri- and postoperative mortality and morbidity, including anorectal, sexual and urinary dysfunction when compared with abdominal surgery [1–3].

Currently, the prevailing opinion for patients diagnosed with early rectal cancers is that local excision should be limited to favourable T1N0 tumours [1,4,5], however increasing data suggest that due to tumour downstaging, preoperative radio(chemo)therapy may provide an opportunity for expanding the applicability of local excision to more advanced tumours [6–15]. To date, the results are difficult to fully interpret due to highly selective entry criteria and the retrospective nature of most studies. To explore this issue in a systematic fashion, we performed a prospective study. The rationale for trial design, methods and interim analysis has been previously described in detail [15–17]. In brief, two selection criteria were used. The first was that no tumour should be larger than 3–4 cm prior to neoadjuvant treatment. The second was that selection for local excision alone depended on the pathological response to radiation evaluated in local excision specimen. For all patients with radioresistant cancers, characterized by yp ⩾ T2 after neoadjuvant treatment, immediate conversion to radical

☆ Presented at 28th Meeting of European Society for Therapeutic Radiology and Oncology, London, UK, May 2011.

* Corresponding author. Address: Department of Radiotherapy, Maria Sklodowska-Curie Memorial Cancer Centre, W.K. Roentgena 5, 02 781 Warsaw, Poland.
E-mail address: bujko@coi.waw.pl (K. Bujko).

[1] On behalf of The Polish Colorectal Study Group.

0167-8140/$ - see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.radonc.2012.12.005

abdominal surgery was mandated. In this context, the use of preoperative irradiation is not only a treatment, but also a selection test. Specifically, local excision serves as an excision biopsy, which may be either curative, thus sparing the risks of abdominal surgery or indicate residual advanced disease best treated with radical surgery.

Our trial aimed at answering two questions: (i) Does downstaging to ⩽ypT1 after preoperative radiation irrespective of pre treatment stage have an acceptable local recurrence rate? (ii) What is the optimal preoperative radiotherapy schedule?

Patients and methods

The study was granted ethical approval and all patients signed written informed consent. The eligibility criteria included G1–2 adenocarcinoma less than 3–4 cm as assessed by endorectal sonography or by magnetic resonance. In most centres the 3 cm cut-off point was used. It was also deemed that the proximal margin of the tumour should not be higher than 8–9 cm from the anal verge in the case of anterior wall involvement or not higher than 10–12 cm in the case of posterior wall involvement. Inclusion criteria were sessile cT1, cT2 and borderline T2/3 tumours (irregular outer margin of muscularis propia but no obvious perirectal fat invasion). For inclusion it was mandatory that no evidence of mesorectal nodal or distant metastases was present. Polypoid cT1 tumours were excluded from the study as they are likely to be favourable T1 lesions [18]. Of note, the study protocol did not provide mandatory criteria to define node negative, rather this judgment was made according to standard reporting criteria in local centres. The protocol did not mention in its inclusion/exclusion criteria the percentage of circumferential bowel wall involvement, concurrent inflammatory bowel disease, hereditary colorectal cancer syndromes and concurrent malignancy.

Prior to neoadjuvant therapy, 4–5 tattoos of india ink were placed submucosally at the tumour border. Patients were randomly allocated to neoadjuvant radiochemotherapy or short-course radiotherapy. The planned sample size was 102 randomized patients [16]. In both groups, a 6 week interval between radiation and surgery was planned. After local excision, good responders, defined as those with pathological complete response (pCR) or downstaged to ypT1 without unfavourable prognostic factors (positive margin, tumour fragmentation, G3, perineural, venous or lymphatic vessels involvement), were managed by observation alone with close follow up. Patients with initially cT1 tumour pathologically diagnosed as ypT1 without unfavourable prognostic factors were also included into "good responders" category. For those patients with ⩾ypT2 or adverse tumour features, immediate conversion (within 2–3 weeks) to radical surgery incorporating total mesorectal excision was planned. According to the protocol, apart from the randomized patients, the all non-randomized patients, who were treated according to the methods described in the protocol, were prospectively registered and analysed. The non-randomized patients were included in order to increase power of local control evaluation.

In the short-course group, patients received 25 Gy in 5 fractions over one week. After one week interval, 4 Gy external beam boost was added. One week interval was used in order to diminish a risk for acute toxicity. In the chemoradiation group, patients received 50.4 Gy in 28 fractions plus 5.4 Gy external beam boost in 3 fractions. The irradiation technique was identical in the two groups. Details of this technique are described elsewhere [16]. In short, the irradiated volume included rectum, lateral lymph nodes and mesorectum up to the sacral promontory. Such extensive volume was used even for T1–2 tumours as, by definition, only a small volume of mesorectum can be resected using local excision, and we intended to cover all potential areas of occult nodal disease. The boost volume included primary tumour and adjacent mesorectum. Patients in the chemoradiation group received three 2-day cycles of chemotherapy during 1st, 3rd and 5th weeks of irradiation according to the Nordic schedule [19]. Each cycle consisted of bolus (not a short or long infusion) leucovorin 20 mg/m^2 per day and 5-fluorouracil 400 mg/m^2 per day.

Full-thickness local excision was carried out with 0.5–1 cm margin around tattoos. A positive margin was diagnosed when cancer cells were seen at the margin. The exact pathological techniques to analyse residual disease and determine pCR were not standardized. Postoperative chemotherapy was not given. The toxicity was reported using RTOG/EORTC scale [20]. Central quality control for diagnosis, treatment and pathology was not performed.

Clinical examination, pelvic CT (or transrectal EUS), rectoscopy and serum carcinoembryonic antigen level test were performed at 3-month interval during the first 2 years, at 4-month interval during the third year and twice a year thereafter. Abdominal sonography or CT was performed twice a year, chest X-ray once a year and colonoscopy every 3 years.

The chi-square test or Fisher exact test was used to compare proportions and the Mann–Whitney *U* test to compare continuous variables. The Kaplan–Meier method was used to calculate cumulative incidence of local failure. All time intervals were measured from the first day of radiotherapy. A multivariate binary logistic regression with backward elimination was used to evaluate predictors of pathological response to radiotherapy. A multivariate Cox regression analysis with backward elimination was used to evaluate predictors of local recurrence. The data were analysed with SPSS version 19 for Windows (SPSS, Chicago, IL, USA).

Results

Due to poor accrual, the study was terminated prematurely. Between November 2003 and October 2010, 104 patients with previously untreated primary rectal cancers from nine Polish centres were enrolled. The four most active centres entered 93 patients (89.4%). In these centres all patients who fulfilled entry criteria were offered participation and all of them agreed to undergo preoperative radiation and local excision. Fifteen patients (14.4%) were excluded (Fig. 1). The analysis therefore included 89 remaining patients. The radiotherapy schedule was randomized in 51 patients (57.3%). Thirty-eight remaining patients (42.7%) were not randomized, but were treated according to the protocol. The most frequent reason for lack of randomization was poor performance status precluding the use of chemotherapy (Fig. 1); these patients received short-course radiotherapy. Overall, 64 patients (71.9%) received short-course radiotherapy and 25 (28.1%) chemoradiation (Fig. 1). Because the sample of randomized patients was small and eight patients from this group (16%) were actually treated using the opposite than allocated schedule of radiation (Fig. 1), the results were analysed in total group of patients according to the type of radiotherapy received. Additionally, intention-to treat analysis of pathological response to radiation was carried out for randomized patients. Patients' characteristics are shown in Table 1. Patients were older in the short-course group compared to the chemoradiation group, $p = 0.018$ (Table 1).

Deviations from the protocol

Tattoos were not done in 23 patients (27.7%, no data $n = 6$). Deviations from the irradiation schedule were observed in 20 patients (31.3%) from the short-course group and in 12 (48.0%) from the chemoradiation group. In the short-course group, 17 patients (26.6%) did not receive boost. Two patients (8.0%) in the chemoradiation group did not receive boost and one patient did not receive chemotherapy. The remaining deviations were minor.