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CLINICAL INVESTIGATION **Rectum**

EVALUATION OF BIOLOGIC EFFECTIVE DOSE AND SCHEDULE OF FRACTIONATION FOR PREOPERATIVE RADIOTHERAPY FOR RECTAL CANCER: META-ANALYSES AND META-REGRESSION

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Purpose: To evaluate whether the risk of local recurrence depends on the biologic effective dose (BED) or fractionation dose in patients with resectable rectal cancer undergoing preoperative radiotherapy (RT) compared with surgery alone.

Methods and Materials: A meta-analysis of randomized controlled trials (RCTs) was performed. The MEDLINE, Embase, CancerLit, and Cochrane Library databases were systematically searched for evidence. To evaluate the dose–response relationship, we conducted a meta-regression analysis. Four subgroups were created: Group 1, RCTs with a BED >30 Gy_{10} and a short RT schedule; Group 2, RCTs with BED >30 Gy_{10} and a long RT schedule; Group 3, RCTs with BED ≤30 Gy_{10} and a short RT schedule; and Group 4, RCTs with BED ≤30 Gy_{10} and a long RT schedule.

Results: Our review identified 21 RCTs, yielding 9,097 patients. The pooled results from these 21 randomized trials of preoperative RT showed a significant reduction in mortality for groups 1 ($p = .004$) and 2 ($p = .03$). For local recurrence, the results were also significant in groups 1 ($p = .00001$) and 2 ($p = .00001$).The only subgroup that showed a greater sphincter preservation (SP) rate than surgery was group 2 ($p = .03$). The dose–response curve was linear ($p = .006$), and RT decreased the risk of local recurrence by about 1.7% for each Gy_{10} of BED.

Conclusion: Our data have shown that RT with a BED of >30 Gy_{10} is more efficient in reducing local recurrence and mortality rates than a BED of ≤30 Gy_{10}, independent of the schedule of fractionation used. A long RT schedule with a BED of >30 Gy_{10} should be recommended for sphincter preservation.

Rectal cancer, Preoperative radiotherapy, Biologic effective dose, Meta-analysis.

INTRODUCTION

Annually, approximately 41,420 patients are diagnosed with rectal cancer in the United States (1). Surgical resection is the cornerstone of curative treatment. Superficial, invasive, small cancer can be effectively managed with limited surgical procedures, such as local excision. However, most patients have more deeply invasive tumors that require more extensive surgery, such as low anterior or abdominoperineal resection. Others present with locally advanced tumor adherent or fixed to adjoining structures such as the sacrum, pelvic sidewalls, prostate, or bladder. The surgical and oncologic treatment of these patients varies greatly depending on the tumor stage and location within the rectum (2, 3). Strong evidence has shown that preoperative radiotherapy (RT) significantly reduces the incidence of local relapse in patients with resectable rectal cancer. The ability to decrease the incidence of local recurrence in patients with resectable tumors has also been seen when surgery has been optimized according to the total mesorectal excision principles (4). Postoperative RT, even if combined with chemotherapy, has less effect and also is more toxic than preoperative RT, as has been shown in several randomised trials (5–8). The fashions of RT realization have followed two main schools of thought: the French, from the G. Roussi Institute and the Swedish. Both schools performed ''long-term'' RT, split on 4–5 weeks, to achieve a whole dose of 40–55 Gy, followed by surgery, 4–6 weeks from the end of RT, at the earliest (9, 10). The Swedish school also encouraged ''short-term,'' high-dose (5 Gy split/d for 5 days) RT to achieve a whole dose of 25 Gy, followed by surgery, not later than 1 week (11). A number of trials have evaluated these different preoperative RT schedules followed by surgery versus surgery alone in patients with rectal cancer (10–28). At least three meta-analyses have explored the benefit of preoperative RT (29–31). One of them concluded

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that preoperative RT at biologically effective doses (BEDs) of ≥30 Gy reduced the risk of local recurrence and death from rectal cancer (31). However, none of them explored a direct comparison between high or low RT dose fractionation and the BED. Thus, the contribution of our meta-analysis was the use of regression methods to evaluate the risk reduction of local recurrence per unit (Gy_{10}) of BED across a broad range of BEDs.

METHODS AND MATERIALS

Search strategy for identification of studies

In our search strategy, we identified trials listed in one of the following search engines: MEDLINE, CancerLit, EMBASE, or the Cochrane Library, incorporating the Science Citation Index, ISI Science, and Technology proceedings, and current contents databases as far as back as available. In addition, we searched the trial registries and conference proceedings. We scanned the references of the selected articles and previous systematic reviews for any other relevant trials. The search strategy included the following keywords variously combined: rectal neoplasms, colorectal neoplasms, rectal cancer, RT, preoperative, neoadjuvant, RT, radiation, irradiation, and randomized trial. All details regarding the search strategy for the identification of studies have been described in a supplementary file.

Selection criteria

Studies were included in this systematic review of the evidence if they met all the following criteria: patients were randomly assigned to preoperative RT versus surgery alone or an alternative treatment and the study population was well defined. Studies preferably included only rectal carcinoma, defined by tumors located within 15 cm of the pectinate line or anal verge on sigmoidoscopy, or rectosigmoid tumors without metastases. The treatment was clearly described, including radiation dose, fractionation, duration, field size, and RT portals. The timing of surgery after RT completion was clearly set. General surgical principles were described. Compliance with treatment and follow-up were described. The treatment outcomes were reported for overall survival and/or local recurrence.

Types of outcome measures

Overall mortality and local recurrence were pooled in separate analyses for all studies for which data were available. For the calculation of survival and local recurrence, all eligible patients were considered in the denominator, according to the intention to treat. All deaths at the time of reporting, regardless of cause, were included in the survival calculations. Patients with local recurrence included those with nonresected tumors and those with recurrent disease. We used the BED, rather than total physical dose, to compare the different regimens. The BED was calculated according to the time-corrected linear quadratic model of radiation effect (32), which is probably the best available model (33). In this model, $BED = n \times d(1 + [d/\alpha/\beta]) - \alpha/\gamma \times (T - Tk)$, in which n is the number of fractions, d is the dose in Gray per fraction, α/β is the common linear-quadratic quotient (10 Gy), α/γ is the repair rate (0×6 Gy/d), T is the total treatment time in days, and Tk is the proliferation delay (7 days). The choice of coefficients reflected the acute effects. Four subgroups were created to analyze the effect of BED and the schedule fractionation on mortality and local recurrence: Group 1, randomized controlled trials (RCTs) with BED >30 Gy_{10} and short RT schedule (≤5 days; n = 4,402 patients); Group 2, RCTs with BED >30 Gy_{10} and long RT schedules (>5 days; n = 1,096 patients); Group 3, RCTs with BED ≤30 Gy_{10} and short RT schedule (≤5 days; n = 1,439 patients); and Group 4, RCTs with BED ≤30 Gy_{10} and long RT schedules (>5 days; n = 2,150 patients).

Analysis of review

The data analyses were performed using Review Manager, version 4.2 (Cochrane Collaboration (Oxford, Oxfordshire, United Kingdom). All analyses were performed on an intention-to-treat basis. For categorical variables, weighted odds ratios and their 95% confidence intervals were calculated according to the Peto method (34). The results were tested for heterogeneity at a significance level of $p < .05$ according to the methods outlined by DerSimonian and Laird (35). We used linear regression by meta-regression analysis to evaluate the variations between studies, to model the risk of local recurrence as a function of the BED (in Gy_{10}), to test for trends, and to graph the predicted dose–response curve. The BED Gy_{10} for each study was then treated as a continuous independent variable. The dependent variable for regression was the risk of reduction for local recurrence for each study (or equivalently, the percentage of risk reduction of locoregional recurrence = [1 − risk of the local recurrence]), weighted by the inverse of its variance. The coefficient of the BED term in the regression model estimates the slope of the linear BED risk reduction of local recurrence dose–response effect. Solving the regression equation estimates the percentage of risk reduction in local recurrence predicted at any given BED of RT in Gy_{10}.

RESULTS

The electronic and manual searches revealed 2,060 citations. After further screening, 320 full-text articles were retrieved for additional assessment. The reasons for the exclusion of studies are detailed in Fig. 1. A total of 21 studies were ultimately identified that met our meta-analysis inclusion criteria; the total patient population of these studies was 9,087. The details on the treatment modality and treatment volume in the 21 trials included in the analysis are summarized in Table 1.The total radiation dose and fractionation schedules were quite different across the studies, ranging from 5 Gy in a single treatment to >50 Gy within 5 weeks. Combining these trials yielded data on 9,087 patients, 4,532 and 4,555 patients underwent preoperative RT and surgery alone, respectively.

Overall mortality

The effect of adjuvant RT on total mortality (21 RCTs, 9,087 patients) is given in Table 2. Although the effect of treatment on total mortality favored RT in 14 of the 21 trials, a significant difference was observed in only 1 trial. The pooled estimate of the treatment effect was significant (odds ratio [OR], 0.89; 95% confidence interval, 0.81–0.97; p = .01). We performed subgroup analyses to evaluate whether evidence showed a different effect of preoperative RT in predefined subgroups of patients. Of the studies that reported mortality by BED, for overall mortality, the pooled OR was significant in patients with a BED >30 Gy_{10} and short RT schedule (group 1; OR, 0.87; 95% CI, 0.76–0.99; p = .003) and BED >30 Gy_{10} and long RT schedule (group 2; OR, 0.77; 95% CI, 0.61–0.99; p = .04); however, no benefit was seen in those studies with a BED of ≤30 Gy_{10} and