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Mini-review

Efficacy and safety of intraoperative radiotherapy in colorectal cancer: A systematic review

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ABSTRACT

Intraoperative radiotherapy (IORT) has been proposed as an encouraging treatment for colorectal cancer. The aim of this study is to assess the efficacy and safety of IORT for this cancer through a systematic review. Studies located in electronic databases were selected according to established criteria, read and analysed and the results extracted by two independent reviewers. Fifteen studies met the selection criteria. Five-to-six-year local control (LC) was over 80% and 5-year overall survival (OS) was close to 65%. For recurrences, the 5-year overall survival was 30%. The main acute complications were gastrointestinal. Adding IORT to conventional treatment reduces the incidence of local recurrences within the radiation area over 10%. IORT is a safe technique as it does not increase toxicity associated with conventional treatment.

1. Introduction

Colorectal cancer (CRC) accounts for 9.4% of all cancers worldwide, equivalent to 1 million of new cases diagnosed every year. It ranks 4th for men and 3rd for women worldwide. The incidence of colon cancer (CC) is threefold that of rectal cancer (RC), with similar patterns regarding sex for CC and a 20–50% higher incidence in men for RC [1]. The situation in Europe is similar. Incidence of CRC ranks third, representing 13% of all cancers diagnosed in 2006, of which RC cases were approximately 30% [2,3].

Regarding mortality, CRC represented 12% of all cancer deaths in Europe in 2006, ranking just behind lung cancer [2]. CRC has a good overall prognosis and mortality is approximately half its incidence. Five-year overall survival (OS) is 64%, depending mainly on the cancer stage at the moment of diagnosis. For a localised tumor diagnosed at an early stage the 5-year survival is 90%, decreasing drastically to 21% if it has spread [4–6].

The choice of treatment is determined by the appearance of the tumor, the stage and other factors. The therapeutic options include surgery, radiotherapy and chemotherapy. Neoadjuvant radiotherapy is one of the main factors in the treatment for RC as it can eliminate local tumors, reduce their size and facilitate surgery [7]. It is rarely used in the treatment for metastasised CC as its effects are adverse and limit the doses that can be used [8].

CRC presents a high risk of local recurrences. Gastrointestinal tissue tolerance limits the radiation dose to 50 Gy. With intraoperative radiotherapy (IORT), doses can be higher at the moment of surgery without increasing the associated toxicity [9], and do not need to wait some weeks for radiotherapy, making IORT a promising alternative. Some authors state that patients who do not receive IORT relapse within 18 months but with IORT the 3-year local control (LC) increases from 23% to 85% and survival improves (55% versus 24% at 3 years) [10].

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The aim of this study is to asses the efficacy and safety of IORT in the treatment for advanced and recurrent CRC in terms of LC and OS through a systematic review of scientific literature.

2. Material and methods

2.1. Bibliographic search

Scientific literature published between January 2000 and October 2009 was systematically reviewed. The main databases specialised in systematic reviews were used: the *NHS Centre for Reviews and Dissemination*, including HTA (*Health Technology Assessment*), DARE (*Database of Abstracts of Reviews of Effectiveness*) and NHS EED (*Economic Evaluation Database*), and the *Cochrane Library Plus.* General databases such as Medline, Embase, ISI Web of Knowledge (*Institute for Scientific Information*), IME (Spanish Medical Index) and *Tripdatabase* were also searched. In order to locate current research projects, USA database Clinicaltrials.gov and other international registers, such as CCT (Current Controlled Trials), were reviewed. To complete this search process, the databases of other national scientific societies and organisations were reviewed manually in order to add more information of interest. For each database specific search strategies were applied using unique combinations and different variations of free terms.

2.2. Inclusion and exclusion criteria

The recovered studies were read and those that met the previously established inclusion criteria to fit the aims of this study were chosen. The criteria were as follows: (1) regarding the study's design: systematic reviews, meta-analysis, clinical trials, cohort and case-control studies, cross-sectional studies and case series were included; (2) sample size: a minimum of 30 patients treated with IORT; (3) treatment type: patients who received intraoperative electron-beam radiotherapy (IOERT) or X-rays (IORT); (4) results measurement: studies which assessed mortality, morbidity, quality of life, 3–5 years overall survival, disease's LC and short and long-term toxicity; (5) patient type: adults diagnosed with CRC in any stage; (6) patient inclusion period: studies in which the delivery of IORT for most patients was after 1995. This criterion is justified since treatment for colorectal cancer (chemotherapy and radiotherapy) has improved importantly in the last years. If we include studies before 1995 we could attribute outcomes to IORT when they are really originated by other concomitant treatments. Therefore this point helps to improve the comparability among the included studies. (7) Follow-up period: studies with a median follow-up period higher than 3 months; (8) language: only publications in English, French, Italian, Spanish and Portuguese were included.

Two reviewers critically read the selected studies in an independent and blind manner, deciding on final inclusion by consensus. Finally, the most relevant data were rigorous and uniformly extracted into specifically designed evidence tables. In order to assess the quality of the included studies, a scale specifically adapted to CRC was used. This scale had been previously used in studies about IORT in pancreatic cancer [11,12]. It was used in an independent and blind manner by both reviewers and is showed in Table 1. Scoring differences over one point were not allowed and if arisen were resolved by consensus.

3. Results

3.1. Search results and quality of the included studies

The bibliographic search yielded 283 references. After the summaries were read, 30 studies were chosen to be read in their entirety of which 15 met the established selection criteria (Fig. 1). One systematic review was found [13] and the majority of the primary studies were case series except three, which had a comparative design [14–16]. Median follow-up period was over 3 years in only six studies [14,15,17–20], and in two studies it was 5 years [15,18]. Quality of life was analysed in only one study [21]. The sample size was over 100 patients in the majority of the studies and over 200 patients in two studies [18,20]. The studies' countries of origin were mainly European: four studies from the Netherlands [20–23], three from Germany [14,18,24], two from Norway [16,25] and one from Spain [19]. Three studies originated from the United States [17,26,27], two of them from the Mayo Clinic [17,27]; one from Japan [15] and one from Australia [13].

The quality evaluation scale was applied to all studies. The Williams' study obtained the lowest score with 0.5 points [26] and the Mathis' and the Kienle's studies the highest with 8 points [14,17]. The median score was 4.3; five studies obtained scores below average [21,22,24,26,27], 4 of them under 2 points, while most of the remaining studies obtained scores well above average.

3.2. Effectiveness and efficacy

The Skandarajah review, published in 2009, assessed IORT effectiveness on different tumor types, including locally advanced CRC, which have a high possibility of R1 margins after resection. Of the 77 studies included, published between 1968 and 2008, 24 referred to CRC. They considered surgical margins after resection of paramount relevance and found that the 5-year LC with R0 margins oscillated between 70% and 90% decreasing a 20% and a 40% for R1 and R2 margins respectively. Five-year disease-free survival (DFS) was 65%-70% for R0, close to 40% for R1 and less than 10% for R2. The authors conclude that adding IORT to conventional treatments improves LC but not survival [13].

The results of the primary studies are presented according to the stage of the disease; if they are locally advanced primary tumors, recurrent tumors or both. Table 2 reflects the main characteristics of the studies included.

3.2.1. Locally advanced primary tumors (T3–T4)

The Kusters et al. series [20] assessed 290 patients with T3–4 RC and presented the results according to the appearance of R0, R1 or R2 margins after resection. The treatment protocol suffered modifications during the development of the study. Thirty percent of patients received only external preoperative radiotherapy (45–50.4 Gy) during the first years of the study and the other 70% received also postoperative chemotherapy. Five-year local recurrences were 12%. Of these, 94% occurred after IORT was delivered and 54% within the IORT irradiation area. Five-year OS was 66.7% and incidence of metastasis 35%. There were significant differences according to the type of resection (R0 versus R1/2): survival was 73% vs. 31% and metastasis 30% vs. 65%. Mathis and colleagues assessed 146 patients with colon or rectum unresectable tumors (T4N0–2M0), 73% of them in the rectum. External preoperative radiotherapy was delivered to 86% of patients and 90% received 5-FU at the same time. Recurrences developed within the IORT treated area were 3.7% and 17%within the EBRT treatment area. Five-year OS and DFS were 52% and 43% respectively [17]. Likewise, Roeder et al. [18] and Krempien et al. [28] assessed the efficacy of combined treatment on 243 patients with advanced RC (T3-4N+). They observed that within the IORT treated area recurrence was 20% less, showing a 5-year LC of 92%. Also, they observed that patients who received radiochemotherapy (RCT) presented a