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Original article

Role of pelvic radiotherapy for locally advanced rectal cancer and synchronous unresectable distant metastases

Place de la radiothérapie pelvienne dans la prise en charge des patients atteints de cancer du rectum avec des métastases synchrones non résécables

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ABSTRACT

Purpose. – To evaluate the efficacy and safety of pelvic irradiation combined systematic chemotherapy in patients with locally advanced (cT3–T4 and/or cN+) rectal cancer and synchronous unresectable distant metastases.
Patients and methods. – A total of 76 eligible patients who received pelvic radiotherapy and concurrent capecitabine-based chemotherapy were retrospectively reviewed. Patients survival curves were constructed using the Kaplan-Meier method, and a multivariate analysis was performed to identify independent prognostic factors.
Results. – Most of the adverse events were mild during the period of combined chemoradiotherapy. Twenty-two patients experienced resection of primary tumour and 16 patients underwent radical surgery of all lesions. Only five patients had pelvic progression during the follow-up period. The median progression-free survival and median overall survival were 13 and 30 months, respectively. Radical surgery of all lesions following chemoradiotherapy was found to be an independent prognostic factor according to multivariate analysis.
Conclusions. – Pelvic irradiation combined with systematic chemotherapy in patients with locally advanced rectal cancer and synchronous unresectable distant metastases is effective and tolerable, both for pelvic and distant control. A curative resection following chemoradiotherapy was associated with prolonged survival.

Mots clés :
Cancer du rectum
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Radiothérapie pelvienne
Chimioradiothérapie
Résection curative

RÉSUMÉ

Objectif de l'étude. – Évaluer l'efficacité et l'innocuité de l'irradiation pelvienne associée systématiquement à une chimiothérapie chez des patients atteints de cancer du rectum localement évolué (de stade cT3–T4 et/ou avec atteinte ganglionnaire) et de métastases à distance résécables synchrones.
Patients et méthodes. – Les dossiers de 76 patients éligibles qui ont reçu une radiothérapie pelvienne et simultanément une chimiothérapie à base de capécitabine ont été revus rétrospectivement. Les courbes de survie ont été construites en utilisant la méthode de Kaplan-Meier et une analyse multifactorielle a été réalisée pour identifier les facteurs pronostiques indépendants.
Résultats. – La plupart des événements indésirables n'étaient pas sévères au cours de la période de chimiothérapie concomitante. Vingt-deux patients ont eu une résection de la tumeur primitive et 16 patients

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une chirurgie radicale de toutes les lésions. Seuls cinq patients ont été atteints d'une progression pelvienne pendant la période de suivi. La survie sans progression et la survie globale médianes étaient respectivement de 13 et 30 mois. La chirurgie radicale de toutes les lésions après la chimioradiothérapie s'est avérée un facteur pronostique indépendant selon l'analyse multifactorielle.
Conclusions. – L'irradiation et une chimiothérapie systématique chez les patients atteints d'un cancer rectal localement évolué et de métastases à distance résécables synchrones est efficace et bien tolérée, à la fois en termes de contrôle du pelvis et à distance. Une résection à visée curative après la chimioradiothérapie était associée à une longue survie.

1. Introduction

Approximately 20% to 25% of patients diagnosed with rectal cancer present with metastatic disease and have a predicted median survival between 5 months and 6 months without treatment [1–3]. About 80 to 90% of these patients have unresectable metastatic disease and result in a poor prognosis [3–5]. Systematic chemotherapy has been used to be the standard treatment for rectal cancer patients with unresectable metastatic disease and the 5-year survival rate was 30 to 40% in patients who underwent curative resection after chemotherapy [6,7]. Concurrent chemoradiotherapy has been the standard initial treatment for patients with locally advanced rectal cancer since it was proven to be beneficial in reducing the rate of local recurrence and better sphincter preservation [8–12]. Until now, there are insufficient evidences for the use of pelvic radiotherapy in patients diagnosed with locally advanced (cT3–T4 and/or cN+) and synchronous unresectable distant metastases rectal cancer. The primary concern is that although chemoradiotherapy could achieve better local control, it may significantly increase toxicities, which would have a negative impact on subsequent chemotherapy, resulting in inferior outcomes for metastatic lesions.

We conducted this retrospective study to assess the role of pelvic irradiation combined systematic chemotherapy in patients with locally advanced rectal cancer and synchronous unresectable distant metastases from the Fudan University Shanghai Cancer Centre (FUSCC). In addition, we also identified prognostic factors of survival in this group of patients.

2. Patients and methods

2.1. Patient selection

We performed a retrospective study of a consecutive cohort of patients with locally advanced rectal cancer (cT3–T4 and/or cN+) and synchronous unresectable distant metastases, which were treated initially with chemoradiation at the department of Radiation Oncology, Fudan University Shanghai Cancer Centre (FUSCC) between 2008 and 2014. Patients were identified from our institutional patient colorectal cancer database. A total of 76 patients were ultimately enrolled in this study. All of enrolled patients were newly diagnosed with rectal adenocarcinoma confirmed histologically. Patients with unknown TNM stage, those who underwent radiotherapy or chemotherapy only, and those with insufficient or no follow-up data were excluded from this study. The Fudan University Shanghai Cancer Centre Ethics Review Board approved the study.

2.2. Treatment details

Pretreatment clinical stage was assessed on the basis of CT, MRI and/or positron emission tomography (PET). All pretreatment biopsies were reviewed and diagnoses were confirmed by Shanghai Cancer Centre gastrointestinal pathologists. All patients underwent digital rectal examination and proctoscopy to identify the tumour distance from the anal verge. Patients initially received chemoradiotherapy, with a median dose of intensity-modulated radiation of 50.4 Gy (range: 45–54 Gy) delivered to the whole pelvis and rectum and concurrent capecitabine. Sixty patients received capecitabine and weekly oxaliplatin, two patients received capecitabine and weekly irinotecan and eight patients received capecitabine alone. In addition, bevacizumab and cetuximab were used with capecitabine and weekly oxaliplatin in five and one patients, respectively. Patients received a total of 6 months of chemotherapy, whether pre- or postoperative, with the same protocol as the concomitant chemotherapy. If all lesions were evaluated as resectable, patients would be arranged to receive a radical surgery. The sequence of primary tumour and metastases, the type of surgery (lower anterior or abdominal–perineal resection) and whether a temporary colostomy should be performed was at the discretion of each surgeon. It was recommended that patients who could not undergo radical surgery receive maintenance chemotherapy with capecitabine alone. If the tumour progressed, the chemotherapy regimen would be changed to a second-line standard systemic regimen, including 5-fluorouracil (5-FU)/leucovorin/oxaliplatin (FOLFOX4/FOLFOX6) and 5-FU/leucovorin/irinotecan (FOLFIRI). Patients at high risk of obstruction or significant bleeding underwent palliative surgery to remove the primary tumour. The median interval between the completion of chemoradiotherapy and the primary tumour surgery was 12 weeks (range: 7–25 weeks). Standard pathologic tumour staging of the resected specimen was performed after resection in accordance with the guidelines of the College of American Pathologists, with histopathologic diagnosis performed by dedicated gastrointestinal cancer pathologists. Follow-up consisted of routine physical examination with carcinoembryonic antigen measurement and cross-sectional imaging every 2 to 3 months. CT scans of the chest, abdomen and pelvis, full coloscopic evaluation, and/or PET were immediately performed if any symptom of disease occurred or elevated tumour marker levels were detected.

2.3. Evaluation of toxicity and tumour response

Toxicity was evaluated according to the CTC-AE (Common Terminology Criteria for Adverse Events) 3.0 criteria [13]. Tumour response to chemoradiotherapy was evaluated at 2 to 3 months after the beginning of the treatment, including responses of the rectal mass and distant metastases. Tumour response was assessed according to the RECIST criteria [14]. Complete response was defined as complete disappearance of all clinically assessable disease for at least 4 weeks, and partial response as a decrease of at least 30% of the sum of the products of the diameters of measurable lesions for at least 4 weeks. CT scans were done 4 weeks later to confirm a response. Stable disease was defined as a decrease of less than 30% or an increase of less than 20% of measurable lesions, and progressive disease as an increase of at least

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