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Can Diffusion-weighted Magnetic Resonance Imaging Predict Survival in Patients with Cervical Cancer? A Meta-Analysis

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ABSTRACT

Objective: Although diffusion-weighted magnetic resonance imaging (DWI) has been widely used in the diagnosis of cervical cancer, whether it can predict disease recurrence or survival remains inconclusive. This study aimed to systematically evaluate whether DWI can serve as a reliable prognostic predictor in patients with cervical cancer.

Methods: PubMed, the MEDLINE database and the Cochrane Library were searched for DWI studies with >12 months of prognostic data in patients with cervical cancer. Endpoints included tumor recurrence and death. Methodological quality was assessed using the Quality in Prognostic Studies (QUIPS) tool. Combined estimates of hazard ratios (HRs) were derived.

Results: Nine studies involving a total of 796 patients (mean/median age from 45.0 years to 62.9 years) met the inclusion criteria. Methodological quality was relatively high. Eight of the nine studies employed apparent diffusion coefficient (ADC) as an indicator of DWI results. Using disease-free survival (DFS) as an outcome measure, nine studies yielded a combined HR of 1.55 (95% confidence interval (CI): 1.23–1.95), and seven studies that employed pretreatment DWI yielded a combined HR of 1.50 (95% CI: 1.03–2.19), which indicated that unfavorable DWI results were associated with an approximately 1.50–1.55-fold higher risk of tumor recurrence. The two studies investigating the impact of DWI results on overall survival (OS) reported HRs of 7.20 and 2.17, respectively.

Conclusion: DWI may serve as a predictor of tumor recurrence in patients with cervical cancer as showed by meta-analysis, and the quantified ADC as a suitable candidate indicator.

1. Introduction

Cervical cancer is the fourth most common cancer worldwide and presents remarkable mortality, although effective screening has been introduced [1]. The standard therapies for primary cervical cancer include radical hysterectomy, concurrent chemotherapy and radiation therapy, and intracavitary or interstitial brachytherapy [2]. Despite maximal treatment, as described above, the 5-year recurrence rate is reported to be 20–50% for cervical cancer patients. With several known clinical prognostic factors, including tumor size, the International Federation of Gynecology and Obstetrics [FIGO] stage, and pelvic lymph node metastasis, there is still difficulty in explaining the heterogeneity of recurrence among similarly grouped patients [3–5]. Early detection of recurrence could enable the greater personalization of treatment strategies and improve the survival rate [6]. Therefore, exploration for more biomarkers that reliably predict tumor recurrence is needed.

Magnetic resonance imaging (MRI) is now playing an important role in the diagnosis of cervical cancer [7]. Diffusion-weighted magnetic resonance imaging (DWI) is a functional imaging modality that is based on the thermally driven motion of the extracellular water molecules constrained by the tissue microstructure [8]. It provides information in addition to morphology and allows diffusion to be quantified by calculating the apparent diffusion coefficient (ADC). It has been suggested that the ADC may reflect the biologic heterogeneity of tumors by classifying portions with different diffusivities. This therefore provides useful information regarding tumor aggressiveness, subtype characterization and cancer treatment responses [9–11].

More recent studies have reported that DWI might predict tumor recurrence and serve as an independent prognostic factor in cervical cancer. However, the sample sizes of most conducted

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studies have been relatively small, and the ability for DWI to predict recurrence has been remarkably distinct among studies. This meta-analysis aimed to systematically review and statistically estimate the prognostic value of DWI for the survival of patients with cervical cancer.

2. Materials and methods

2.1. Literature search and study selection

This meta-analysis strictly followed the PRISMA statement [12]. Ethical committee approval and patient consent were not required for this research because it was a statistical analysis. Studies were identified by a comprehensive electronic literature search. PubMed, the MEDLINE database and the Cochrane Library (until May 1, 2016) were used to search for English-language articles with the following keywords: (magnetic resonance OR MR) AND (prognosis OR prognostic OR predict OR survival OR recurrence OR relapse) AND (cervical OR cervix) AND (tumor OR cancer OR carcinoma) AND (diffusion weighted OR apparent diffusion coefficient OR ADC). Two reviewers independently checked the abstracts of retrieved publications and obtained the full text of each potentially eligible article. The reference lists reported in the retrieved articles were also screened with extensive checking to supplement the computerized search. Disagreements were resolved by discussion.

Studies that were eligible for inclusion in this meta-analysis met the following pre-specified criteria: (1) used DWI to investigate the prognosis of patients with primary cervical cancer, with or without measuring the ADC; (2) reported a mean or median follow-up time more than 12 months, >=1.5 T MRI scanners, and a minimal sample size of ten; (3) employed at least one reliable endpoint, such as recurrence or death; and (4) reported a hazard ratio (HR) or clinical data that allowed the HR to be calculated. Case reports, conference abstracts, comments, and letters to the editors were excluded.

2.2. Quality assessment and data extraction

To evaluate the methodological quality of the included studies, two reviewers independently assessed each study using the Quality in Prognostic Studies (QUIPS) tool, which is a validated method for assessing the risk of bias in prognostic factor studies [13]. The tool examines a specific checklist, including six important areas: study participation, attrition, prognostic factor measurement, confounding measurement and account, outcome measurement, in addition to analysis and reporting for each study. Each domain was rated as “high risk of bias”, “moderate risk of bias” or “low risk of bias” according to the standards listed in detail. Disagreements were resolved by discussion between the reviewers and re-examination with a senior investigator.

The impact of DWI on survival was measured by a HR between the survival distributions of two groups. The following data were extracted using a standardized data extraction form: (1) basic characteristics of the study, including sample size, patient age, tumor histology, outcome, MRI parameters, and specific criteria of diagnosis; (2) methodological details that needed to be examined with the QUIPS tool; and (3) a HR with its 95% confidence interval (CI) or clinical raw data that could be used to calculate the HR of DWI. For the studies that did not provide multivariate-adjusted HRs, the estimate from univariate analysis was included in the calculation [14]. For studies that reported more than one HR of DWI-related parameters, the one that showed significance in the statistical model was employed in the meta-analysis.

2.3. Data analysis and statistical methods

Briefly, for each study, the log HR and standard error could be calculated (i) by using the unadjusted HR and confidence intervals (CI) directly from each article, (ii) from individual patient data that were provided in some studies or (iii) from extracting cumulative survival data from published Kaplan–Meier plots using the method described by Parmar et al. [15]. The combined HR of the included studies was pooled by a meta-analysis performed using Stata (version 12.0).

We employed the Q statistic to examine the heterogeneity among the included studies. I^2 can be calculated from Q statistics, with I^2 values of 25%, 50%, and 75% representing mild, moderate, and severe inconsistency, respectively. A random-effects model was applicable with an I^2 value of over 50%, and a fixed-effects model was applicable with an I^2 value of less than 50% [16,17]. If heterogeneity was detected, a meta-regression analysis and sensitivity analysis were performed to identify possible sources of the high degree of heterogeneity of the estimates.

By convention, a summary HR greater than 1.0 suggests a worse survival for the group of patients with unfavorable DWI results. This impact of DWI on survival was considered statistically significant if the 95% CI for the combined HR did not overlap 1.0. Statistical significance for hypothesis testing was set at the 0.05 two-tailed level.

Publication bias was assessed using plots of the study results against the precision of the study (funnel plots). Symmetry of the funnel plot was determined using both Begg’s rank correlation test and Egger’s regression test. An asymmetrical funnel plot would suggest potential bias [18].

3. Results

3.1. Study selection and characteristics

The detailed study selection process is shown in Fig. 1. The initial search yielded 39 potentially eligible articles written in English. Eighteen were considered candidates after a careful review of the abstracts. After reading the full text of these articles, nine were excluded for the following reasons: measuring the diagnosis of recurrence or treatment responses without prognostic results (n = 3) [19–21], lack of raw data required to calculate a HR (n = 5) [22–26], or investigating a clinical cohort with a substantial overlap after careful identification (n = 1) [27]. Only one of the two studies by Park et al. was included [28] because the patient cohort in the first study had a similar origin to that used in the second study [27]. The included study reported the HR of pre-treatment ADC on multivariate regression analysis, which was more accordant with the other included trials [28]. Two studies by Nakamura et al. were included after a careful identification of patient groups because the tumor histology, age and statistical results all differed [32,33]. Finally, a total of 9 studies were included in the analysis [6,7,28–34].

The principal characteristics of the 9 publications are outlined in Table 1. A total of 796 patients were included. The median sample size was 83 (range 42–171), and the mean age ranged from 47.2 to 62.9 years old. Seven studies investigated the prognostic value of DWI for disease-free survival (DFS), and two studies investigated the prognostic value of DWI for both DFS and overall survival (OS).

Table 2 shows the main characteristics of MRI extracted from the included studies. The included trials all used 1.5 T or 3 T scanners. Eight of nine studies employed ADC as an indicator of DWI results. Six studies evaluated the prognostic value of DWI before treatment, one study evaluated DWI after completion of treatment [28], and two studies measured DWI related parameters both before and after treatment [30,32]. In the study by Nakamura et al., Cox’s