Human Pathology (2016) **53**, 91–96

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Original contribution

Medullary carcinoma in the colorectum: a systematic review and meta-analysis☆

Jung-Soo Pyo MD, PhD[a], Jin Hee Sohn MD, PhD[a,*], Guhyun Kang MD, PhD[b]

[a]*Department of Pathology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul 03181, Republic of Korea*
[b]*Department of Pathology, Inje University Sanggye Paik Hospital, Seoul 01757, Republic of Korea*

Received 8 January 2016; revised 11 February 2016; accepted 17 February 2016

Keywords:
Medullary carcinoma;
Colorectum;
Clinicopathological characteristics;
Meta-analysis;
Survival

Summary Medullary carcinoma (MC) is a very rare variant of colorectal carcinoma (CRC). Its clinicopathologic findings are not fully elucidated. The aim of this study was to investigate the clinicopathological characteristics of MC in the colorectum through a systematic review and meta-analysis. The meta-analysis examined the incidence, age, sex, site, mismatch repair deficiency (MMRd), MMR protein expression, ARID1A expression, *BRAF*^{V600E} mutation, *KRAS* mutation, and survival rate of MC. The 21 469 CRCs included 462 MCs in 16 eligible studies, representing an estimated incidence of MC of 0.027 (95% confidence interval [CI] 26 0.016–0.045). MC frequently occurred in female patients and in the right colon. Lymph node metastasis of MC was significantly lower than that of poorly differentiated adenocarcinoma/undifferentiated adenocarcinoma (PDA/UDA). In addition, MC had a higher MMRd rate (0.892, 95% CI 0.758–0.956), higher *BRAF*^{V600E} mutation rate (0.652, 95% CI 0.143–0.954) and lower *KRAS* mutation rate (0.171, 95% CI 0.065–0.378) than PDA/UDA and conventional adenocarcinoma. Patients with MC had significantly better overall survival rate compared to patients with PDA/UDA (hazard ratio 0.441, 95% CI 0.262–0.742). However, there was no significant difference of overall survival rate between MC and conventional adenocarcinoma patients. MC predominantly occurred in females and in the right colon, and had different molecular characteristics and behaviors compared to PDA/UDA and conventional adenocarcinoma.

1. Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer mortality worldwide [1]. In the World Health Organization (WHO) classification, colorectal adenocarcinoma (AdCa) includes several variants, such as cribriform comedo-type AdCa, medullary carcinoma (MC), micropapillary carcinoma, mucinous AdCa, serrated AdCa, and signet ring cell carcinoma [1]. Each variant is diagnosed by specific histologic features, and several variants can be admixed within a tumor. In addition, each variant has different clinicopathological characteristics, tumor behaviors, and prognosis.

The incidence of MC in colorectum has been reported as 0.03% of sporadic colorectal carcinoma [2]. MC was previously recognized as large cell AdCa with minimal differentiation or solid-type poorly differentiated carcinoma [3]. MC features sheets of malignant cells with vesicular nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm exhibiting prominent intraepithelial lymphocyte infiltration [1]. Although

☆ Conflict of Interest: none

* Corresponding author at: Department of Pathology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 29 Saemunanro, Jongno-gu, Seoul 03181, Republic of Korea.
E-mail address: jhpath.sohn@samsung.com (J. H. Sohn).

http://dx.doi.org/10.1016/j.humpath.2016.02.018
0046-8177/

MC is morphologically similar to poorly differentiated AdCa (PDA) and undifferentiated AdCa (UDA), MC has a more favorable prognosis compared to PDA and UDA [4].

Although previous studies have reported the clinicopathological characteristics of MC [2–17], conclusive information is not available in the colorectum. The present systematic review and meta-analysis addressed the clinicopathological characteristics and the correlation between MC and survival using eligible studies.

2. Materials and methods

2.1. Published studies search and selection criteria

Relevant articles were obtained by searching the PubMed and MEDLINE databases through November 30, 2015. These databases were searched using the following key words: "colon", "rectum", "colorectal", "medullary carcinoma", "solid type poorly differentiated carcinoma", or "large cell minimally differentiated carcinoma". The titles and abstracts of all searched articles were screened for exclusion. Review articles were also screened to find additional eligible studies. Articles were included if the study was performed in human colorectal cancer and if there was information about the clinicopathological characteristics of MC. Articles were excluded if they were case reports or non-original articles, or if the article was not written in English.

2.2. Data extraction

Data from all eligible studies were extracted by two independent authors. The included data were extracted from each of the eligible studies [2–17]: the first author's name, year of publication, study location, number of patients analyzed, and information for age, sex, site, lymph node metastasis, mismatch repair deficiency (MMRd), immunohistochemical expressions of MMR protein, ARID1A immunohistochemical expression, *BRAF*^{V600E} and *KRAS* mutation status, and overall survival rate.

2.3. Statistical analyses

To perform the meta-analysis, all data were analyzed using the Comprehensive Meta-Analysis software package (Biostat, Englewood, NJ, USA). We investigated the incidence and various clinicopathological characteristics of MC in colorectum for meta-analysis. Eligible studies were divided into studies including PDA/UDA or overall types, and subgroup analyses were performed. Heterogeneity between the studies was checked by the Q and I^2 statistics and expressed as P-values. Additionally, sensitivity analysis was conducted to assess the heterogeneity of eligible studies and the impact of each study on the combined effect. For quantitative aggregation of survival results, the correlation between MC and survival was analyzed according to the hazard ratio (HR) using one of three methods. In studies not quoting the HR or its confidence interval (CI), these variables were calculated from the presented data using the HR point estimate, log-rank statistic or its P-value, and the O-E statistic (difference between the number of observed and expected events) or its variance. If those data were unavailable, HR was estimated using the total number of events, number of patients at risk in each group, and the log-rank statistic or its P-value. Finally, if the only useful data were in the form of graphical representations of survival distributions, survival rates were extracted at specified times to reconstruct the HR estimate and its variance under the assumption that patients were censored at a constant rate during the time intervals [18]. The published survival curves were read independently by two authors in order to reduce reading variability. The HRs were then combined into an overall HR using Peto's method [19]. In the meta-analysis, because eligible studies used various diagnostic criteria and populations, the application of random-effects model rather than fixed-effects model was more suitable. For the assessment of publication bias, Begg's funnel plot and Egger's test were used. If significant publication bias was found, the fail-safe N and trim-fill tests were additionally conduced to confirm the degree of publication bias. The results were considered statistically significant at $P < .05$.

3. Results

3.1. Selection and characteristics of the studies

One hundred twenty-five reports were identified in the database search. Among them, 109 studies were excluded because they involved other diseases (n = 78), insufficient/no information (n = 16), non-English (n = 13), and use of animals or cell lines (n = 2). Finally, 16 studies were included in this systematic review and meta-analysis (Fig. and Table 1). These studies included 21 469 CRC patients, among whom 462 were MC patients.

3.2. Systematic review and meta-analysis

The incidence rate of MC in the eligible studies varied from 0.1% to 65.7%. In those eligible studies that included overall types, the estimated incidence of MC was 0.027 (95% CI 0.016–0.045). However, the incidence rate of MC was markedly higher (23.1%) among PDA/UDA of the colorectum. MC was frequent in females (0.678, 95% CI 0.606–0.743) and in the right colon (0.868, 95% CI 0.811–0.909) compared to PDA/UDA and conventional AdCa. The rate of lymph node metastasis in PDA/UDA was 0.800 (95% CI 0.681–0.882), while the rate in MC was significantly lower (0.298, 95% CI 0.093–0.638) (Table 2). However, there was no age-related difference between MC and other tumor types.