RESEARCH ARTICLE

TNM Stages and Prognostic Features of Colorectal and Mucinous Adenocarcinoma Patients: a Meta Analysis

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Abstract

Aim: The significance of the mucinous adenocarcinoma in TNM staging and prognosis for colorectal tumor patients is still controversial. The aim was to provide a meta-analysis for TNM staging and prognostic features of colorectal tumors. Methods: 30 individual case-control studies were finally included into this meta-analysis, involving a total of 444,489 cancer cases and 45,050 mucinous adenocarcinomas, of relations with TNM staging and prognostic features. Results: Compared to non-mucinous adenocarcinoma patients, the TNM IV stage accounted for a larger percentage of mucinous adenocarcinomas (OR=1.48, 95%CI 1.28-1.71, POR<0.001) and the prognosis was significantly poor (HR=1.06, 95%CI 1.04-1.08, P<0.001). After heterogeneity testing, the results was similar to the holistic approach outcome (HR=1.48, 95%CI 1.35-1.62, P<0.001). Conclusion: Compared to patients with non-mucinous adenocarcinomas, mucinous adenocarcinoma patients with later TNM staging make up a big percentage, and mucinous adenocarcinoma is an independent risk factor for poor prognosis.

Keywords: Mucinous colorectal adenocarcinoma - TNM - prognosis - meta-analysis

Asian Pacific J Cancer Prev, **13**, 3427-3430

Introduction

Colorectal cancer is a common malignancy (Huang et al., 2012), in which, mucinous adenocarcinoma is a relatively uncommon. The definition of mucinous adenocarcinoma was that the mucus is more than 50% in adenocarcinoma according to World Health Organization (WHO) (Jass et al., 1989), and the mucinous adenocarcinoma was 1.5%-25.4% of all colorectal cancer (Papadopoulos et al., 2004; Pande et al., 2008). With the deeply study of biological behavior and pathological features of colorectal cancer, we recognized the pathological types and prognosis were closely related. However, the influence of mucinous adenocarcinoma on TNM staging and prognosis of colorectal cancer is still in dispute. Kang et al found that the TNM staging of mucinous adenocarcinoma patients was late, but it didn't affect the prognosis compared to other adenocarcinoma, based on the large sample research of U.S National Cancer Institute database (SEER) (Kang et al., 2005). Yamaguchi et al (2012) also supported this result. However, some other findings showed that mucinous adenocarcinoma was an independent prognostic risk factor (Kanemitsu et al., 2003; Catalano et al., 2009; Ghabeljoo et al., 2011). Some studies showed that mucinous adenocarcinoma might reduce the sensitivity of radiotherapy and chemotherapy in recent years (Negri et al., 2005; Sengul et al., 2006). At present, there are few studies about mucinous adenocarcinoma in China, and most studies suggested that the patients with mucinous adenocarcinoma had late stage and poor prognosis (Songqing et al., 2002; Miao et al., 2005; Safaee et al., 2010). In our study, we performed Meta analysis on TNM staging and prognostic features of colorectal cancer patients, aimed at a comprehensive assessment of mucinous adenocarcinoma.

Materials and Methods

Literature search

We searched the Google scholar, PubMed, Cochrane Library and CNKI (China National Knowledge Infrastructure) databases for all relation studies before Mar 2012. The following key words were used:muc in and (colorectal OR colon OR rectum OR rectal) and (cancer OR carcinoma OR adenocarcinoma OR neoplasm OR malign). We recruited data from published papers and abstracts without restriction of language.The reference lists of reviews and retrieved articles were hand searched at the same time. In the case of more than one article was published by the same author using the same case series, the latest published results were used.

Eligible Studies

Two investigators reviewed all identified studies independently to determine whether an individual study was eligible for inclusion.The following criteria were

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used to include published studies: (1) TNM stages and prognostic features of colorectal and mucinous adenocarcinoma patients; (2) sufficient data were presented to calculate the odds ratios (ORs) and 95% confidence intervals (CIs).

Data Extraction

Two investigators extracted the data independently, and the result was reviewed by a third investigator. The following characteristics were collected from each study:first author, years of publication, ethnicity (country) of study population, the number of patients and controls for a study.

Statistical Analysis

The strength of the relationship between body mass index and lung cancer risk in patients never and active smokers was estimated by ORs with 95% CI under a homozygote comparison.The distribution of genotypes in the included studies was tested for HWE using the χ^2 test. We also quantified the effect of heterogeneity by the Q-test and I^2 test. I^2 ranges between 0 and 100%.and I^2 values of 25, 50 and 75% were defined as low, moderate and high estimates, respectively. When a significant Q-test ($P<0.10$) or $I^2 > 50\%$ indicated heterogeneity across studies, the random effects model was used for meta-analysis, or else the fixed effects model was calculated. Begg's test was used to provide evidence of publication bias,which was shown as a funnel plot ($P<0.05$ was considered a significant publication bias).Analyses were conducted using Stata 12.0 (Stata Corporation, College Station, TX, USA). All P values are two-tailed.

Results

The general results of selected literature

There are 3759 English literatures in original search, after exclusion and screening, 28 English literatures (Cusack et al., 1996; Sun et al., 1996; Wu et al., 1996; Enriquez et al., 1998; Cerottini et al., 1999; Consorti et al., 2000; Nozoe et al., 2000; Kanemitsu et al., 2003; Chen et al., 2004; Du et al., 2004; Papadopoulos et al., 2004; Kang et al., 2005; You et al., 2006; Grillo-Ruggieri et al., 2007; Hill et al., 2007; Lee et al., 2007; Farhat et al., 2008; Pande et al., 2008; Catalano et al., 2009; Min et al., 2009; Song et al., 2009; Xie et al., 2009; Sultan et al., 2010; Catalano et al., 2011; Jivapaisarnpong et al., 2011; Hyngstrom et al., 2012; Langner et al., 2012; Yamaguchi et al., 2012) and 2 Chinese literatures (Songqing et al., 2002; Miao et al., 2005) meet the requirements. In the 30 literatures, 21 literatures can be used for Meta analysis of the relationship of mucinous adenocarcinoma and TNM staging, including 444489 cases, in which mucinous adenocarcinoma were 45050 cases, accounting for 10.1% of all cases; 21 literatures can be used for Meta analysis of relationship of mucinous adenocarcinoma and prognosis, including 450804 cases, in which mucinous adenocarcinoma were 45354 cases, accounting for 10.1% of all cases. In the 30 literatures, the least cases were 70, the most cases were 244794; the earliest publication was in 1996, and the latest

Table 1. Generally Data of Study

Author	Publishing year	Study design	Randomized method	Allocation concalment	Double-blind	withdraw	Analysis outcomes	cases	mucinous adenocarcinoma(%)
Catalano	2009	RCT	Unclear	Unclear	Yes	Yes	prognosis	255	19
Catalano	2011	RCT	Unclear	Unclear	No	Yes	prognosis	1025	17.4
Cerottini	1999	RCT	Unclear	Unclear	No	Yes	prognosis	851	27.9
Chen	2004	RCT	Unclear	Unclear	No	Yes	Stage	2619	5.5
Consorti	2000	RCT	Unclear	Unclear	No	Yes	Stage,prognosis	248	11.7
Cusack	1996	RCT	Unclear	Unclear	No	Yes	prognosis	186	10.3
Du	2004	RCT	Unclear	Unclear	Yes	Yes	Stage,prognosis	15762	3.9
Enriquez	1998	No-RCT	Unclear	Unclear	No	Yes	Stage	142	19
Farhat	2008	RCT	Unclear	Unclear	No	Yes	Stage,prognosis	70	4.5
Grillo-Ruggieri	2007	RCT	Unclear	Unclear	Yes	Yes	prognosis	136	18
Hill	2007	RCT	Unclear	Unclear	No	Yes	prognosis	77	62
Hyngstrom	2012	RCT	Unclear	Unclear	No	Yes	Stage,prognosis	244794	10.4
Jivapaisarnpong	2011	RCT	Unclear	Unclear	No	Yes	Stage	427	4.7
Kanemitsu	2003	RCT	Unclear	Unclear	No	Yes	Stage,prognosis	2678	3.6
Kang	2005	RCT	Unclear	Unclear	No	Yes	Stage,prognosis	164628	10.3
Langner	2012	RCT	Unclear	Unclear	Yes	Yes	Stage	300	14.7
Lee	2007	No-RCT	Unclear	Unclear	No	Yes	prognosis	5022	5.9
Min	2009	RCT	Unclear	Unclear	No	Yes	Stage,prognosis	4519	6.1
Nozoe	2000	RCT	Unclear	Unclear	Yes	Yes	Stage,prognosis	283	7
Pande	2008	RCT	Unclear	Unclear	No	Yes	Stage,prognosis	753	1.6
Papadopoulos	2004	RCT	Unclear	Unclear	No	Yes	Stage,prognosis	1160	25.4
Song	2009	RCT	Unclear	Unclear	No	Yes	Stage,prognosis	2079	6.9
Sultan	2010	RCT	Unclear	Unclear	No	Yes	prognosis	159	22
Sun	1996	RCT	Unclear	Unclear	No	Yes	Stage	287	11.1
Wu	1996	RCT	Unclear	Unclear	Yes	Yes	Stage	510	10.4
Xie	2009	No-RCT	Unclear	Unclear	No	Yes	Stage,prognosis	1380	13.6
Yamaguchi	2012	RCT	Unclear	Unclear	No	Yes	Stage	4306	4.2
You	2006	RCT	Unclear	Unclear	No	Yes	prognosis	5138	9.8
Songqing Yen	2002	No-RCT	Unclear	Unclear	No	Yes	Stage	947	11.3
Miao Zhen	2005	RCT	Unclear	Unclear	No	Yes	Stage	1715	11.5

RCT, randomized controlled trial

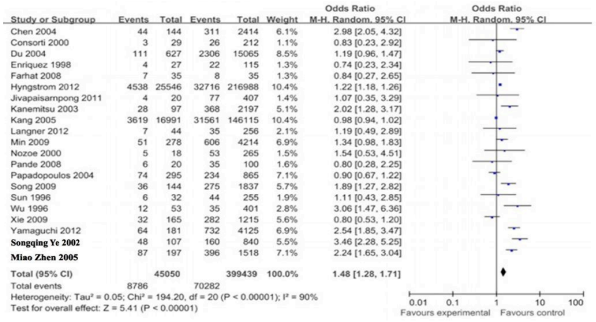

Figure 1. The Meta-analysis in TNM IV Stage of Mucinous Adenocarcinoma and Non-mucinous Adenocarcinoma

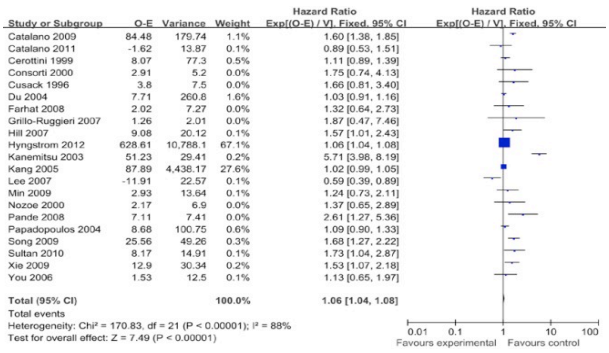

Figure 2. Meta-analysis of Mucinous Adenocarcinoma Prognosis

was in 2012 (Table 1).

Meta-analysis of mucinous adenocarcinoma and TNM staging

In this study, we examined the proportion of TNM stage IV in mucinous adenocarcinoma, due to the heterogeneity (P<0.001), we used a random effect model. With meta-analysis, the OR value was 1.48 (95% CI: 1.28-1.71; P<0.001), which means compared to non-mucinous adenocarcinoma patients, the TNM later staging of the patients with mucinous adenocarcinoma had larger proportion (Figure 1).

Meta-analysis of Mucinous Adenocarcinoma Prognosis

With meta-analysis, the HR value was 1.06 (CI: 1.04-1.08; P<0.001), which suggests that mucinous adenocarcinoma patients had worse prognosis compared to non-mucinous adenocarcinoma patients. Due to the heterogeneity (I^2=88%; P<0.001), we removed the large heterogeneity literatures, including Du et al. (2004), Hyngstrom et al. (2012), Kane mitsu et al. (2003), Kang et al. (2005), Lee et al. (2007), Papadopoulos et al. (2004), then the heterogeneity was reduced significantly (I^2=33%; P=0.1), the analysis results were consistent with previous overall analysis, the HR value was 1.48 (CI: 1.35-1.62; P<0.001), suggesting that the meta-analysis results are accurate and reliable (Figure 2).

Discussion

We confirmed that there were differences about staging and prognosis between mucinous adenocarcinoma and non-mucinous adenocarcinoma by meta-analysis. Although some studies indicated that the difference of staging was not obvious (Jivapaisarnpong et al., 2011;Verhulst et al., 2012), in our study, the mucinous adenocarcinoma patients with late TNM staging accounting for large proportion (OR: 1.48, 95% CI: 1.28-1.71) compared to non-mucinous adenocarcinoma patients, through a comprehensive analysis of the latest research in China; mucinous adenocarcinoma might have the features of late finding and fast progress, which was consistent with most studies(Chen et al., 2004; Du et al., 2004; Hyngstrom et al., 2012). Therefore, early diagnosis is very important for mucinous adenocarcinoma patients, there are many molecular biological differences between mucinous adenocarcinoma and non-mucinous adenocarcinoma, such as MMR protein deficient (Chiang et al., 2010), microsatellite instability (MSI) (Greenson et al., 2009). Using molecular biomarkers to diagnose colorectal cancer may be able to improve the rate of early diagnosis of mucinous adenocarcinoma. Compared with non-mucinous adenocarcinoma, whether mucinous adenocarcinoma is an independent prognostic risk factor is still in dispute, some studies suggest that mucinous adenocarcinoma is only related to late staging, not an independent prognostic risk factors (Kang et al., 2005; Yamaguchi et al., 2012). In this study, the survival data were collected from various research, through meta-analysis, the HR value was 1.06 (CI: 1.04-1.08), suggesting the prognosis was poor in mucinous adenocarcinoma patients, although the difference of prognosis was not obvious, the HR value was only 1.06, there were still significant difference (P<0.001); therefore, we believe that mucinous adenocarcinoma is an independent prognostic risk factor for colorectal cancer. This result may be associated with reducing the sensitivity of radiotherapy and chemotherapy by mucinous adenocarcinoma (Negri et al., 2005; Sengul et al., 2006). We should pay more attention to the mucinous adenocarcinoma patients, the patients who were confirmed should be performed radical resection, and expanding the dissection range of lymph node, these organs which have been infiltrated should be performed resection too. Presacral space infusion chemotherapy should be used to prevent local recurrence after surgery; strengthen follow-up, once the local recurrence appears, performing a second surgery to improve the survival rate of mucinous adenocarcinoma patients (Songqing et al., 2002).

In this study, there are still some shortcomings: firstly, the definition of mucinous adenocarcinoma has a subtle difference in different studies, for example, Wu et al. (1996) defined it as "the mucus is more than 60%", which is different with the definition of WHO. Secondly, the published year of literatures spans from 1996 to 2012, the treatment of patients in different studies are different. At last, our meta-analysis exist heterogeneity, we removed the articles which have larger heterogeneity, and the results are consistent with the overall analysis.

In summary, we believe that the mucinous adenocarcinoma patients with late TNM staging accounting for large proportion compared to non-mucinous adenocarcinoma patients, and mucinous adenocarcinoma is an independent prognostic risk factor.

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