RESEARCH ARTICLE

Ki-67/MIB-1 as a Prognostic Marker in Cervical Cancer - a Systematic Review with Meta-Analysis

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Abstract

Background: In cervical cancer patients it has been reported that there in a significant Ki-67/MIB-1 expression is correlated with survival in cervical cancer patients. However, the prognostic value is still not well understood. Materials and Methods: In the present meta-analysis the prognostic value of Ki-67/MIB-1 with regard to overall survival (OS) and disease-free survival (DFS) in cervical cancer was investigated. The databases of PubMed, ISI Web of Science, Cochrane Central Register of Controlled Trials, EMBASE, Science Direct and Wiley Online Library were used to identify appropriate literature. Results: In order to explore the relationship between Ki-67/MIB-1 and cervical cancer, we have included 13 studies covering 894 patients in the current meta-analysis. The effect of Ki-67/MIB-1 on OS for pooled random effects HR estimate was 1.63 (95% confidence interval (CI) 1.09-2.45; P<0.05). The pooled HR for DFS was 1.26 (95%CI 0.58-2.73; P>0.05) and the subgroup analysis indicated Ki-67/MIB1 was associated with DFS (HR=3.67, 95%CI 2.65-5.09) in Asians. Conclusions: According to this meta-analysis, Ki-67/MIB-1 has prognostic value for OS in patients suffering from cervical cancer. For better evaluation of the prognostic role of Ki-67/MIB-1 on DFS, studies with larger numbers of patients are needed to validate present findings in the future.

Keywords: Cervical cancer - Ki-67/MIB-1 - prognosis - meta-analysis

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Introduction

Cervical cancer is the fourth most common cancer among women. Median age of diagnosis is about 52 years, but has a bimodal distribution with picks at 35 to 39 and 60 to 64 years of age. Annually 500000 death is caused by cervical cancer all around the world. In Europe, a total of 58,373 new cases of cervical cancer and 24,385 deaths were reported in 2012. The overall incidence rate of cervical cancer in Europe is 10.6 per 100,000 (Jemal et al., 2011; Kesic et al., 2012; Ghojazadeh et al., 2013). Surgery, chemotherapy and radiotherapy are the main treatment methods where mostly are used in association with other methods for cervical cancer. However, the long term prognosis of cervical cancer is still poor, with expected 5-year survival rate less than 10% (Jabbari et al., 2012; Yaghoubi et al., 2012; Amirnia et al., 2014; Eskander and Tewari, 2014).

Cervical cancer is still one of the main problems in women health field worldwide. Even with considering best available therapies, many patients will die due to metastasis or other consequences of cervical cancer (Andrae et al., 2012). Relation between human papilloma virus infection and dysplasia and cervical carcinoma has been known as a scientific fact (Chaturvedi et al., 2011). Human papilloma virus infection in cervical cells' leads to functional changes of host genes and investigating these genes can play an important role in screening and diagnosing cervical cancer (Ghojazadeh et al., 2012a; Ghojazadeh et al., 2012b; Azami-Aghdash et al., 2013; Naghavi-Behzad et al., 2013; Sushma et al., 2014). These functional changes cause changes in cellular cycle which appears through abnormal manifestation of proteins related to this cycle, such as Ki-67 (Ikenberg et al., 2013; Rostamizadeh et al., 2013; Ghojazadeh et al., 2014). Ki-67/MIB-1 is known as predictive factor for tumor development and its expression is correlated with poor prognosis in several types of cancer, such as breast cancer and non-small-cell lung carcinoma (Azambuja et al., 2007; Azami-Aghdash et al., 2013; Rahimi-Ardabili et al., 2012; Fakhrjou et al., 2013; Karami et al., 2013; Mohammadzadeh et al., 2013; Aliasgarzadeh et al., 2014; Shams-Vahdati et al., 2014). Ki-67 status in different tumoral cells and its correlation with prognosis has always been a controversial and significant field of research.

In a study investigating Ki-67 levels and prognosis in

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triple negative breast cancer it had been concluded that, high levels of Ki-67 is associated with more aggressive clinical features, Also it was suggested that Ki-67 can be used as a factor to classify triple negative breast cancer in order to recognize prognostic and response characteristics (Keam et al., 2011). In another study focusing on predicting value of Ki-67 on prognosis in bladder cancer it had been concluded that Ki-67 labeling index may be a precise predictor for poor prognosis in patients with bladder cancer (Sugino et al., 2011). In contrast, according to another study it has been reported that the increased labeling of Ki-67 was not associated with poor outcomes in cervical carcinoma patients of stage I (Van de Putte et al., 2004).

Although lymph node status and pathological features of primary tumor and FIGO stage are thought to be relevant to the prognosis of cervical cancer, considering the fact that the clinical value of Ki-67 for prognostication of cervical cancer is still doubtful, In this meta-analysis it is tried to reveal the impact of Ki-67/MIB-1 on overall survival (OS) and/or disease-free survival (DFS) in cervical cancer.

Materials and Methods

Selecting publications and inclusion criteria

In this meta-analysis, studies which had investigated the association between Ki-67/MIB-1 and prognosis in cervical cancer, published during 2000-2014. Libraries such as PubMed, ISI Web of Science, EMBASE, Cochrane Central Register of Controlled Trials, ScienceDirect and Wiley Online Library were searched using the following keywords: "*cervical cancer*", "*cervical neoplasm*", "*prognosis*", "*Ki-67*", "*MIB-1*", "*proliferation*", "*survival*". Inclusion criteria for the studies was composed of: *i)* Studies published in English. *ii)* Studies in which patients with cervical cancer are included. *iii)* Studies which has investigated correlation between Ki-67expression and the prognosis in cervical cancer. *iv)* Studies with a clear and precise definition of target population (clear inclusion and exclusion criteria). *v)* Clearly stated or calculable Hazard ratios (HR) and 95% CI for OS or DFS. *vi)* To avoid duplication, If 2 studies had included same samples of patients in several publications, the latest study was chosen.

To extend our search range, the reference list of all identified studies was inspected. All the titles and abstracts of included studies were read by 4 experienced researchers to exclude irrelevant ones. Then, full-texts of the studies were inspected by researchers to see as if the study is included. In case of any disagreements occurred in the suitability of studies, the fifth researcher was included among researchers, then researchers would conduct a discussion until a consensus is finally reached.

Data extraction

Four authors extracted the required information from publications precisely. The following data were collected from each study: published year, first author's name, number of patients, antibody detecting Ki-67/MIB-1, defined cut-off values, follow-up period, and required data to evaluate the relationship between the expression of Ki-67/MIB-1 and OS and/or DFS. No minimal number of patients was defined to include a study in present meta-analysis, nor a minimal duration of median follow-up. Flow diagram of study is shown in Figure 1. The following exclusion criteria were implemented in all studies: *i)* Any research articles but original research articles were excluded. *ii)* Studies with no control group. *iii)* Articles with duplicated data. *iv)* Articles with no usable data.

Statistical methods

Based on the cut-off points given in the articles by the authors, the expression of Ki-67/MIB-1 was divided into two groups (negative and positive). The expression of Ki-67/MIB-1 on survival was evaluated using HRs to quantitatively aggregate the survival rates. After calculating or extracting HRs and their 95% confidence intervals (CIs) the relationship of prognosis and Ki-67/MIB-1 expression was inspected. The log-rank statistic or its P-value, the HR value estimate and the O-E statistic or its variance was used to recover the estimated HR value and its variance. Based on the outcome provided in the initial publication the HR was evaluated in every study. If any of the mentioned parameters could not be extracted, the case of patients exposed to the risk in each group, the log-rank statistic or the P-value and the whole number of the events were searched to calculate an approximation of the HRs. Engauge Digitizer software was used to extract survival-relative data at stipulated time points from figures. The HRs and its standard error (SE) were reconstructed with filling spreadsheets with HR calculations in order to estimate HRs from published summary statistics (Parmar et al., 1998).

Survival charts were analyzed independently by 4 people to reduce the inaccuracy. If survival was defined for more than two groups (e.g. several cut-off values were used to divide the patients into different groups based on Ki-67/MIB protein expression), we combined the data of some groups in order that we can make a comparison between two groups. For each study, the OS and/or DFS were analyzed. Considering subgroups such as ethnicity (Africans, Europeans or Asians) and various treatments (surgery and RT) HR was calcualted.

All the data analyses were performed with the software of STATA 8.2 (StataCorp, College Station, Tex). Using the method reported by Yusuf S et al, the individual HRs were combined into an overall HR (Yusuf et al., 1985). Statistical heterogeneity was measured using the Q statistic ($p<0.10$ was set as representative of significant statistical heterogeneity). A random-effects model was used if the Q-tests implied that there existed heterogeneity between the studies, Also subgroup analysis was used to investigate any source of heterogeneity. The publication biases was estimated using Begg's funnel plot. If P value was>0.05, it was confirmed that no publication biases was found.

Results

Literature search and characteristics of the included studies

Table 1. Main Characteristics of All Studies Included in the Meta-Analysis (Overall Survival)

First Author(publication year)	Total patients	Median follow-up (months)	Antibody	Threshold	Hazard ratio (95%CI)
Bahnassy AA (2007)	43	NR	MIB-1	1% (PI)	1.53 (1.03-20.7)
Ho DM (2000)	97	83.4 (mean)	MIB-1	55% (LI)	3.62 (1.3-10.09)
Klimek M (2011)	122	5y	Anti-Ki-67	52% (PI)	2.28 (1.27-4.11)
Oka K (2000)	75	NR	Anti-MIB-1	40% (PI)	3.4 (0.53-22.15)
Shiohara SI (2005)	103	65.1 (mean)	Anti-Ki-67	50% (PI)	1.57 (0.53-4.66)
Shiohara SII (2005)	103	65.1 (mean)	Anti-Ki-67	50% (PI)	1.44 (0.32-6.39)
Sultana H (2003)	30	5y	Anti-Ki-67	33% (LI)	0.46 (0.04-5.99)
Suzuki M (2000)	67	78	Anti-MIB-1	26.4% (PI)	0.49 (0.15-2.53)
Yang M (2014)	180	64 (mean)	Anti-Ki-67	10% (PI)	3.80 (1.80-4.70)
Zhang T (2012)	40	NR	Anti-Ki-67	34.62% (PI)	3.44 (0.7-18.34)
Zhang T (2012)	48	NR	Anti-Ki-67	32.74% (PI)	3.04 (0.73-13.26)

CI: confidence interval; NR: not reported; y: years. PI: proliferation index; LI: labeling index

Table 2. Main Features of All Studies Included in the Meta-Analysis (Disease-Free Survival)

First Author (publication year)	Total patients	Median follow-up (months)	Antibody	Threshold	Hazard ratio (95%CI)
Bahnassy AA(2006)	38	13(mean)	NR	NR	1.38(0.66-2.87)
Graflund MIN+(2002)	37	222(mean)	MIB-1	1%(PI)	0.30 (0.10-0.91)
Graflund MIIN+(2002)	37	222(mean)	MIB-1	1%(PI)	0.28(0.01-0.85)
Klimek M(2011)	122	5y	Anti-Ki-67	52%(PI)	1.19(1.05-3.50)
Oka K(2000)	75	NR	Anti-MIB-1	40%(PI)	4.88(0.42-55.98)
Yang M(2014)	180	64(mean)	Anti-Ki-67	10%(PI)	3.80(2.50-4.90)

CI: confidence interval; NR: not reported; y: years; PI: proliferation index

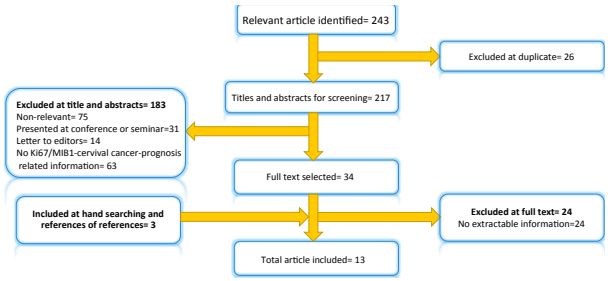

Figure 1. Flow Diagram of Studies Included in the Meta-Analysis

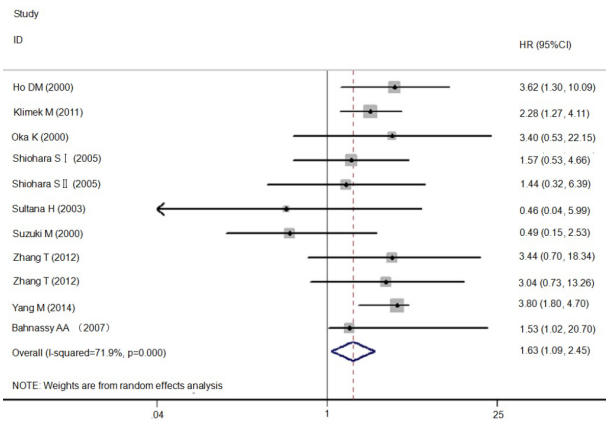

Figure 2. Results of the Meta-Analysis with All Evaluable Studies for Overall Survival

In present study 13 studies including 894 patients were identified, which had been published between 2000 and 2014 (Ho et al., 2000; Oka et al., 2000; Suzuki et al., 2000; Graflund et al., 2002; Sultana et al., 2003; Shiohara et al., 2005; Bahnassy et al., 2006; Bahnassy et al., 2007; Klimek et al., 2011; Zhang et al., 2012a; Zhang et al., 2012b; Yang et al., 2014). All studies had used indirect hemaggultination reaction to detect antibodies. Anti-Ki67 and MIB-1 were applied to detect the Ki-67 expression. Main characteristics of included studies for met-analysis of OS and DFS are shown in Table 1 and 2, respectively. Subgroup analyses were performed in all 8 studies with ethnicity and treatment.

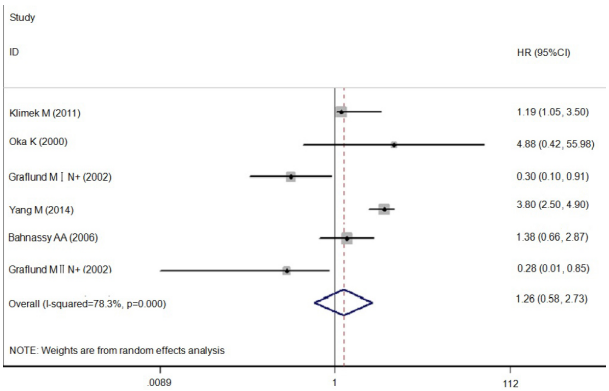

Figure 3. Results of the Meta-Analysis With All Evaluable Studies For Disease Free Survival

Meta-analysis

The meta-analysis results of OS is shown in Figure 2. Eleven studies used immunohistochemistry (IHC) for OS, the pooled random HR was 1.63 (95%CI 1.09-2.45; P<0.05), with significant evidence of heterogeneity between studies (I^2=71.9%, Q=2.36, P<0.05). Restricting analysis to ethnicity, data failed to show a correlation in

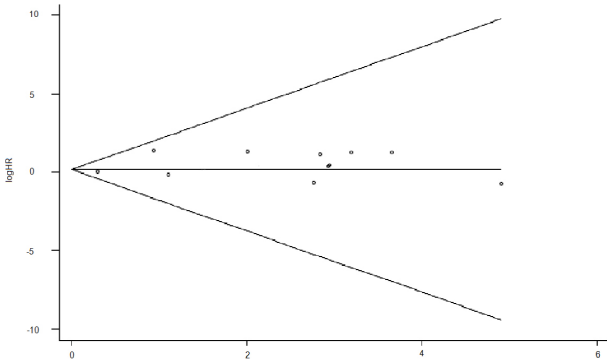

Figure 4. Begg Test was Performed with Pseudo 95% Confidence Limits to Detect the Publication Bias Risk of Overall Survival (P=0.907)

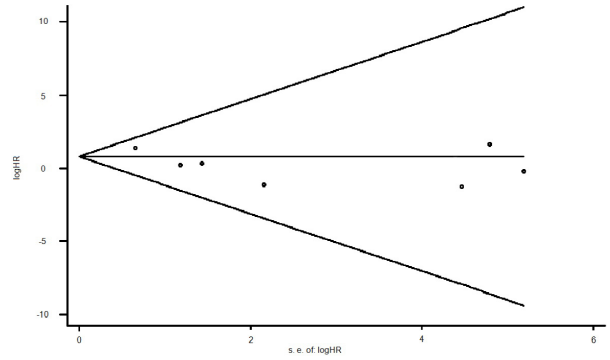

Figure 5. Begg Test was Performed with Pseudo 95% Confidence Limits to Detect the Publication Bias Risk of DFS (P=0.014)

Africans (HR=1.53, 95%CI 0.34-6.86) and Europeans (HR=1.29, 95%CI 0.74-2.23). But statistically difference was observed in Asians (HR=1.53, 95%CI 1.04-3.23). By treatment subgroup analysis, no dramatic differences were discovered in surgery (HR=1.97, 95%CI 0.78-4.99) or RT treatment (HR=1.56, 95%CI 0.93-2.63). The meta-analysis results of DFS is shown in Figure 3. Seven studies assessed DFS with the pooled random HR of 1.26 (95%CI 0.58-2.73; P>0.05) and there was evidence for heterogeneity (I^2=78.3%, Q=0.59, P>0.05). Altogether, six studies were assessed ethnicity. The subgroup analysis revealed that Asians was associated with DFS (HR=3.67, 95%CI 2.65-5.09). Whereas, no association was found in Europeans (HR=0.81, 95%CI 0.39-1.67). Of 5 studies eligible for treatment subgroup, analysis of these data showed that DFS was not positively associated with surgery (HR=1.13, 95%CI 0.71-2.24) and RT (HR=1.26, 95%CI 0.71-2.24).

To evaluate the meta-results stability sensitivity analyses were performed. For OS and DFS, the results indicated that random effects estimate before and after the deletion studies were similar. Also publication bias statistics were determined by using the method of Begg's test. No publication biases were found in 11 OS on studies (P=0.907) (Figure 4); But significant difference in 6 studies on DFS (P=0.014) (Figure 5).

Discussion

As far as Ki-67/MIB-1 is closely integrated with cell proliferation, it has been known as a tumor marker in cancers due to its close correlation with cell proliferation. It has been concluded that Ki-67/MIB-1 expression is associated with poor prognosis (Ho et al., 2000; Oka et al., 2000; Suzuki et al., 2000; Costa et al., 2001; Sultana et al., 2003; Bahnassy et al., 2007; Klimek et al., 2011; Zhang et al., 2012a; Zhang et al., 2012b; Yang et al., 2014). Based on results of present study Ki-67/MIB-1 can be used as a predictor of prognosis because of its profound correlation with prognosis.

Detailed cell cycle analysis has revealed that Ki-67/MIB-1 is present in the nuclei of cells in the G1, S, G2 and mitosis phases. However, the mechanism for the Ki-67 gene expression is still unknown. Although some studies has revealed possible or partial mechanisms responsible for Ki-67/MIB-1 expression; for example in a study it was proven that p53-binding motifs intervened part of the transcriptional suppression of Ki-67 promoter through an interaction with p53 , also p53 was able to suppress the Sp1-stimulated Ki-67 promoter activity (Wang et al., 2011).

There has been many studies investigating the relationship between Ki67/MIB-1 expression and prognosis in different types of cancers; such as ovarian cancer (Battista et al., 2014), breast cancer (Goldhirsch et al., 2013), esophageal squamous cell carcinoma (Hu et al., 2011), lung cancer (Warth et al., 2014), colorectal cancer (Peng et al., 2013), glioblastoma (Smith et al., 2012) and prostate cancer (Tollefson et al., 2014). All mentioned studies indicated that which indicated that Ki-67/MIB-1 expression was associated with poor prognosis so it can be used as a prognostic predictor might be used as a potential predictor for the survival of patients with some cancers.

No biases were found in OS studies, while it was shown that there were biases for DFS (Figure 4 and 5). The main point which might have affected present meta-analysis is strict exclusion criteria for this study, for example by excluding non-English studies many studies bearing prominent results were excluded.

The techniques used to detect the expression of Ki-67 /MIB-1 might have been another source of bias. In present meta-analysis, not always the antibody used to stain Ki-67 were the same (Table 1 and 2). It has been shown that using equivalent antibodies appeared to make differences in variable staining features (Lindboe and Torp, 2002; Lindboe et al., 2003). It has been proven that MIB-1 antibody is the most suitable antibody to detect Ki-67, because it has the highest sensitivity and give the clearest staining when compared to other available antibodies (Fasanella et al., 2011; Lindboe et al., 2003). Also a positive ki67 staining of the tumor cells was confirmed when it was compare with positive nuclear staining for a standard sample. So using different antibodies and a protocol to count the stained cells without a confirmed standard may lead to a variance in results.

Another potential source of biases, might be due to HR variations resulted from extrapolation of survival-relative data when no HR existed, using Kaplan-Meier model. Although for certain articles HR was directly extracted using the original data provided in study. Considering this

as a potential source of bias, four independent persons analyzed the data extracted from Kaplan-Meier model, then extrapolated the HR to reduce variability. Then estimated HR were compared with the original results, but no variances were found.

In present meta-analysis, different cut-off points were used to apply it in definition of cervical cancer with a positive Ki-67/MIB-1. It is difficult to determine a standard critical cut-off values in clinical practice, because sometimes median or arbitrary cut-off value are selected. It has been already confirmed that using minimum P-value approach to select cut-off value may result in significant biases in conclusions (Altman et al., 1994). Ki67 labelling indices tend to cluster around values ending with 5 or 0 both in cases where the values were acquired by counting the fraction of stained tumor cell nuclei by estimation (Cserni et al., 2014). Although it seems more standard for analysis of prognostic markers to define the expression levels based on median, but it might lead to loss of information (Altman et al., 1994). In a study investigating role of Ki-67 proliferative index in predicting overall short-term survival in patients with typical and atypical pulmonary carcinoid tumors it was concluded that Ki67 index cut-off value of 5% can perform best for predicting overall survival while satisfying both specificity and sensitivity (Walts et al., 2012). In another study about breast cancer (Spyratos et al., 2002) using different Ki-67/MIB-1 cut-offs, it was concluded that a Ki-67/MIB-1 cut-off of 10% was optimal to classify tumor (high and low proliferation indexes) in therapeutic trials. Also a Ki-67/MIB-1 cut-off of 25% was optimal to detect highly proliferative tumors (Spyratos et al., 2002). In summary, a suitable threshold is still needed for Ki-67/MIB-1 to certify for cervical cancer.

Except Ki-67/MIB-1 positivity status, other features of disease may influence the survival; such as tumoral cell grade, metastasis, lymph node involvement. Unfortunately in present study just the univariate prognostic value of Ki-67/MIB-1 was investigated. So it is really difficult to jump to conclusions before considering other factors. In order to overcome this limitation prospective studies with larger population are needed.

In conclusion, Ki-67/MIB1 is considered as a prognostic marker in cervical cancer. According to the results that patients with high Ki-67/MIB1 expression had significantly less OS than patients with low expression of Ki-67/MIB1 ($P<0.001$). Although considering possible sources of biases it is necessary that studies with programmed design to overcome biases needs to be conducted, to offer a better conclusion about the relationship between Ki-67/MIB1 and prognosis of patients with cervical cancer.

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