RESEARCH ARTICLE

Prognostic Significance of p53 in Gastric Cancer: a Meta-Analysis

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Abstract

    <u>Background</u>: Gastric cancer is one of the frequently seen cancers in the world and it is the second most common reason for death due to cancer. The prognostic role of expression of p53 detected by immunohistochemistry in gastric cancer remains controversial. This meta-analysis aimed to explore any association between overexpression and survival outcomes. <u>Materials and Methods</u>: We systematicarly searched for studies investigating the relationships between expression of p53 detected by immunohistochemistry and prognosis of gastric cancer patients. Study quality was assessed using the Newcastle-Ottawa Scale. After careful review, survival data were extracted from eligible studies. A meta-analysis was performed to generate combined hazard ratios for overall survival and disease-free survival. <u>Results</u>: A total of 4.330 patients from 21 studies were included in the analysis. Our results showed tissue p53 overexpression in patients with gastric cancer to be associated with poor prognosis in terms of overall survival (HR, 1.610; 95% CI, 1.394 -5.235; p:<0.001). Pooled hazard ratio for disease free survival showed that p53 positivity or negativity were not statitistically significant (HR, 1.219; 95%CI, 0.782-1.899; p:0.382). <u>Conclusions</u>: The present meta-analysis indicated overexpression of p53 detected by immunohistochemistry to be associated with a poor prognosis in patients with gastric cancer.

Keywords: p53 - prognosis - gastric cancer - meta-analysis

Introduction

    Gastric cancer is one of the frequently seen cancers in the world and it is the second most common reason of death due to cancer (Parkin et al., 2002). Incidence of gastric cancer varies among countries and even in different regions of the same country (Torres et al., 2013). It is known as a progressive disease. Surgical resection is the only potentitial curative therapy but the disease recurs in an important part of the patients despite adjuvant or neoadjuvant chemotherapy/chemoradiotherapy (Cunningham et al., 2006). A long-term survival can not be obtained by palliative chemotherapy in inoperable or metastatic or disease (Glimelius et al., 1997).

    All of the three therapy modalities administerd in patients with gastic cancer have potential harmful side effects. Protection of patients from the negative effects of therapy and individualising the therapy is one of the important targets of therapy in gastric cancer today. After use of trastuzumab - that has beeen developed against Human Epidermal Growth Factor Receptor 2 (HER2) that shows a positivity rate of 12-24% in gastric cancer - in metastatic gastric cancer, individualised therapy started gaining popularity in gastric cancer (Tanner et al., 2005). Prognostic factors determined at diagnosis help in assessment of the intensity of the therapy and are also directive in targeted-therapy. One of the prognostic factors in gastric cancer is p53 (Sezer et al., 2013).

    p53 plays an important role in cell cycle arrest and induction of apoptosis. It is a tumor supressor gene that inactivates in development of many malignancies including gastric cancer. Expression rate of p53 detected by immunohistochemistry is reported as 13-54% in gastric cancer (Ochiai et al., 2006; Karim, 2014). p53 shows nuclaear staining due to accumulation of mutant p53 which is resistant to degradation. A cell without mutation does not show immunohistochemical staining of p53 because there is no such accumulation in the cell (Pietrantonio et al., 2013).

    Prognostic role of p53 expression in gastic cancer has been searched in many studies. In some studies it has been suggested that patients without expression of p53 have a longer survival and p53 is a bad prognostic factor (Begnami et al., 2010; Goncalves et al., 2011; Ye et al., 2012). Contrary to these studies some studies show that p53 expression has no relation with survival and other

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clinicopathological parameters (Murakami et al., 2007; Lazar et al., 2010; Tsujitani et al., 2012).

Results of the studies about the role of p53 as a prognostic factor in gastric cancer is contradictory. Because of this, prognostic significance of the abnormal increase of p53 expression detected immunohistochemically in gastric cancer is searched in this study.

Materials and Methods

Search strategy

A systematic search using the following keywords, "p53 or TP53", "cancer or carcinoma", "gastric" and "prognosis" was performed through the PubMed database. The last search was updated in July 2013. The language of the publications was confined to English and only the human studies were searched. The search was broadened by browsing the related summary, methods and references of retrieved articles.

Inclusion and exclusion criteria

All studies needed to meet the following criteria for the meta-analysis: (1) case reports and collected work were not included in the study (2) case-control studies were included in the study (3) studies searching the prognostic significance of p53 expression in gastric cancer were included (4) studies in which expression of p53 was searched by a method other than immunohistochemistry were excluded (5) studies without a summary of statitistical analysis including data of effect size of p53 in terms of survival were excluded (6) duplicated studies were excluded (7) studies written in only English were included in this study.

Studies selected

Two independent rewiewers (MY, OD) evaluated the studies and selected the ones to be included in the meta-analysis. Abstracts of all of the studies found by search of database were reviewed. Full-text format of the stuides thoght to be included in the meta-analysis were found. Full-text format of the studies that were included in the meta-analysis were reviewed, and summarised statistical data were extracted from the studies that were in full-text format.

Study population

Patients with gastric cancer, sufficient follow-up period and that the p53 expression was detected by immunohistochemical method were included in the study. When patients who were enrolled in different studies by the same authors were identified, the study with the higher quality was included in the meta-analysis.

Quality assessment of the studies

Quality of the stuides were evaluated by two independent reviewers (MY, VK) by using the Newcastle-Ottawa Quality Assessment Scale which is used in evaluation of non-randomised studies. In this scale, selection of patient population, comparability of the study and the follow-up results of the study are evaluated. A star between 0 and 9 is suggested for the studies according to

these three different titles. In quality assessment 9 stars is considered as the highest quality (Wells et al., 2003). Discordant studies were evaluated by the two reviewers together in order to come to an agreement about all of the items about the studies.

Data extraction

Data was extracted independently by two reviewers from the studies included in the meta-analysis. The incompatibility between the two reviewers were fixed by evaluating the studies together after data extrction and they cama to an agreement about all of the items (1) basic information about the study, first author, the year of study, and the country (2) study design (3) demographic data such as the the distrubion of the patients according to sex (4) details of the treatment, stage of the disease in the patients included in the study (5) Information about life span such as 5-year overall survival rate (OS) and disease-free survival (DFS) were extracted from the studies included in the meta-analysis.

Statistical analysis

The primary aim of the statitical analyses we used in our study was to search the effect of - positivity or negativity of overexpression of p53 detected by immunohistochemistry- on survival rate. For each study Hazard Ratio (HR) eas calculated with 95% Coincidence Interval. HR>1 and not including 95% Coincidence Interval1 were considered significant. When HR was not reported, it was calculated with spesific statistical data determined by data extraction.

Homogeneity was evaluated by using χ^2-based test of homogeneity test and inconsistency index (I^2). It was considered as heterogeneity when p value was <0.10 or I^2 was >50% for χ^2. Results were given regardless of heterogeneity or homogeneity by using both random model and fixed model. For brief HR the P value<0.05 was considered as statistically significant. Publication bias was examined by using Egger's regression intercept, Begg-Mazumdar rank correlation analysis, and a visual inspection of funnel plot (16.17). Statistical analyses were performed by using Comprehensive Metaanalysis V 2.0.

Results

Study eligibility

Through electronic screening, 472 potentially relevant articles consistent with our searching terms were identified and 376 of them were elimintaed after reading the abstracts. Of the 96 article that were in full-text format 50 were excluded because of not including survival data, 20 were excluded since there were no spesific result about p53 and 5 were excluded because the data was not enough for evaluation. The flowchart of selecting procedure and the exclusive reason of studies are summarized in Figure 1. A total of 21 studies were included in the meta-analysis (Table 1).

Quality assessment of the studies

Quality assessment of the 21 studies inclueded in the meta-analysis was performed by using Newcastle-Ottawa

Scale. In this quality assessment system, scores 1-3, 4-6 and 7-9 are accepted as low, medium and high quality respectively. Median score of the studies included in the meta-analysis was found as 6.

Characteristics of the patients and p53 expression

A total of 4330 patients were included in the meta-analysis. 2496 (62.4%) of the patients were male and 1488 (37.6%) were female. Female/male ratio was 0,6. Median p53 cut-off value was 10%. Positivity rate of p53 was found as 41.9% when all of the studies were evaluated together.
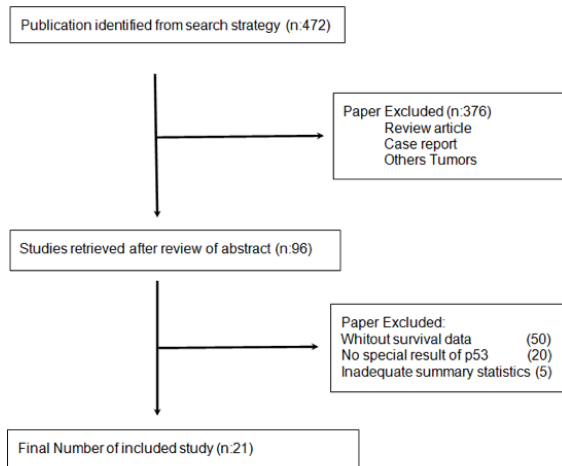
Overall survival

Pooled hazard ratio for overall survival (OS) indicated that p53 positivity is related with OS (HR, 1.610; 95% CI, 1.394-5.235; p<0.001; Figure 2). Studies enrolled in teh meta-analysis were found significantly heterogenous (p<0.001 I²:81.540) and therefore pooled hazard ratio for OS was calculated by using random effect model.

Disease-free survival

Only two studies including hazard ratio and summary of statistics to calculate hazard ratio were enrolled in the meta-analysis for (DFS). Pooled hazard ratio for DFS showed that p53 positivity or negativity were nort statitistically significant (HR, 1.219; 95%CI, 0.782-1.899; p:0.382; Figure 3). Studies enrolled in the meta-analysis for DFS were found significantly heterogenous (p:0.001 9 I²:81.821) and therefore pooled hazard ratio random effect model was used for DFS.

Publication bias

An important publication bias was identified for OS (Begg's test, p0.04; Egger test, p<0.001). Also the Funnel Plot graphics for OS indicated a publication bias (Figure 4). It was calculated that 435 contrariwise studies were needed in order to invalidate the results of the meta-analysis. Since only two studies for DFS were enrolled in the meta-analysis publication bias for this could not be evaluated.

Figure 1. Flow Chart of the Meta-Analysis

Table 1. Summary Table of Studies Included in Meta-Analysis; NR:Not Reported; a: not Reported Adjuvan Threapy

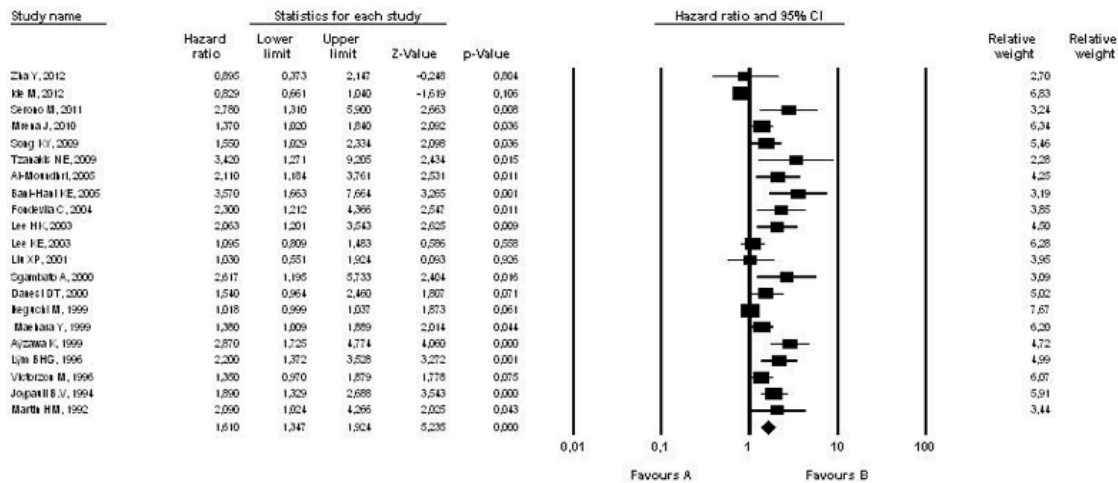| Study	HR	Low limits	Upper limits	Country	Total Number of Patients	Stage	Treatment	Cut of Level (%)	P53 Positive Ratio	Study Qulatiy Score	Conclusion
Zha Y, 2012	0.895	0.376	2.164	China	136	Stage 1-3	paklitaxel/ kapesitabin	10	64.7	6	Positive
Ide M, 2012	0.829	0.661	1.041	Japan	192	Stage 1-4	Surgeya	10	39.1	5	Negative
Serono M, 2011	2.78	1.31	5.90	Spain	44	Stage 1-4a	Surgey-Adjuvan McDonald	10	65.9	7	Positive
Mrena J, 2010	1.37	1.02	1.84	Finland	336	Stage 1-4	Surgeya	20	31	5	Positive
Song KY, 2009	1.55	1.029	2.334	Korea	157	Stage 3	Surgeya	10	54.7	6	Positive
Tzanakis NE, 2009	3.420	1.270	9.200	Greece	93	Stage 1-4	Surgeya	15	67.7	5	Positive
Al-Moundhri, 2005	2.11	1.18	3.75	Sultanate of Oman	121	Stage 1-4	NR	10	53.7	4	Positive
Bani-Hani KE, 2005	3.57	1.66	7.65	Jordan	89	Stage 1-4	Surgeya	5	51.7	6	Positive
Fondevila C, 2004	2.3	1.21	4.36	Spain	156	Stage 1-4	Surgey/ Surgey Mitomicin Tegafur	10	45.5	8	Positive
Lee HK, 2003	2.063	1.201	3.542	Korea	308	Stage1-4	Surgeya	10	34.1	6	Positive
Lee KE, 2003	1.095	0.808	1.482	Korea	841	Stage1-4	Surgeya	15	43.2	7	Positive
Liu XP, 2001	1.03	0.55	1.92	Japan	190	Stage 1-4	Surgeya	20	42.1	6	Negative
Sgambato A, 2000	2.617	1.195	5.735	Italy	96	Stage 1-2	Surgeya	30	9.4	7	Positive
Danesi DT 2000	1.54	0.96	2.45	Italy	137	Stage1-3	Surgeya	10	48.9	6	Negative
Ikeguchi M, 1999	1.018	0.999	1.037	Japan	97	Stage 2	Surgeya	10	47.4	6	Positive
Maehara Y, 1999	1.3803	1.0034	1.8787	Japan	427	Stage1-3	Surgeya	10	38.6	6	Positive
Aızawa K, 1999	2.87	1.72	4.76	Japan	221	Stage1-3	Surgeya	10	29.7	6	Positive
Lım BHG, 1996	2.2	1.4	3.6	Australia	116	Stage1-4	Surgeya	5	23	7	Positive
Victorzon M, 1996	1.35	0.97	1.88	Finland	242	Stage 1-4	Surgeya	20	39	6	Positive
Joypaull BV, 1994	1.89	1.33	2.69	United Kingdom	206	Stage1-4	Surgeya	NR	46	6	Positive
Martin HM, 1992	2.09	1.02	4.25	United Kingdom	125	Stage1-3	Surgeya	NR	57	5	Positive

Figure 2. Random-Effects Model of Hazard Ratio (95% Confidence Interval) of OS Associated with p53 Positive (Favours B) versus p53 Negative (Favours A)
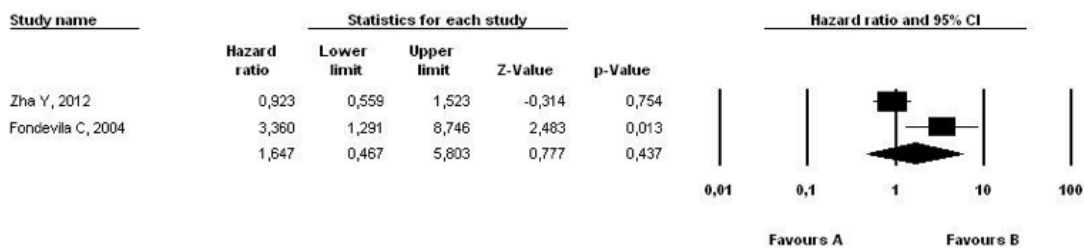

Figure 3. Random-Effects Model of Hazard Ratio (95% Confidence Interval) of DFS Associated with p53 Positive (Favours B) Versus p53 Negative (Favours A)
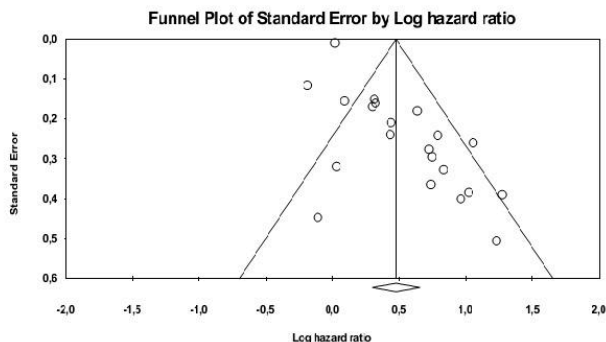

Figure 4. Publication Bias Determination Using Funnel Plot

Other progostic factors

Four studies (Bani-Hani et al., 2005; Song et al., 2009, Tzanakis et al., 2009; Sereno et al., 2012) including hazard ratio and summary of statistics to calculate hazard ratio were enrolled in the meta-analysis for stage. Pooled hazard ratio for OS showed that stage was statitistically significant (HR, 1.843; 95%CI, 1.663-2.044; p<0.001).

Only two studies (Ide et al., 2012; Maehara et al., 1999) including hazard ratio and summary of statistics to calculate hazard ratio were enrolled in the meta-analysis for Lymphatic invasion. Pooled hazard ratio for OS showed that Lymphatic invasion positivity or negativity were nort statitistically significant (HR, 0.627; 95%CI, 0.416-0.944; p:0.026).

Three studies (Ide et al., 2012; Maehara et al., 1999, Aizawa et al., 1999) including hazard ratio and summary of statistics to calculate hazard ratio were enrolled in the meta-analysis for vascular invasion. Pooled hazard

ratio for OS showed that vascular invasion positivity or negativity were nort statitistically significant (HR, 1.018; 95%CI, 0.788-1.316; p:0.889).

Discussion

p53 plays an important role in control of cell cycle and apoptosis which has a meaning of fall of yellow leaves in fall. p53 mutation occurs in more than 50% of lung, breast, colon and other common tumors. In gastric cancer mutation and overexpression rates of p53 are found to vary according to stage of the disease (Hollstein et al., 1991). The relation of overexpression of immunohistocemically detected p53 with prognosis is indefinite in gastric cancer.

Meta-analysis is a useful searching method by which results of different studies about the same subject are synthesized and reanalyzed. In this meta-analysis results of 4330 patients enrolled in 21 different studies were evaluated. p53 expression was found significantly related with OS. A relation between DFS and p53 expression could be searched only in two studies and a significant relation was not found.

Distinctive heterogeneity of the studies enrolled in the meta-analysis is the first and the most important problem of our analysis. The reason of the heterogeneity of the studies enrolled in the meta-analysis may be the differences of age, histological type of tumor, grade, stage, size of tumor and therapy in patients. Excision method of the tissues (surgical or endoscopic excision) evaluated for p53 expression may have affected this result also. The second most important problem of the meta-analysis is publication bias. The most important reason of publication

bias may be that the PubMed database was searched electronically and the language of the publications was confined to English. Another reason is the tendency of publicating the studies with positive results only in English international journals. Only three studies of the meta-analysis demonstrated negative results and the reason for this may be that studies with negative results are not published in English international journals. However the highness of the number of the studies needed to invalidate the results of our meta-analysis may demonstrate the capacity of our meta-analysis.

The third problem of our meta-analysis is that all the studies enrolled are retrospective studies. Data of the many of the studies were obtained by examining the patient files retrospectively and detecting p53 expression of tissues that were excised during surgery. This may have caused patient choice bias.

p53 expression is not only a prognostic factor but also a predictive factor of response to therapy in gastric cancer. It has been demonstrated that p53 expression is a predictive factor both for surgical and platinum-based therapies (Liu et al., 2012).

Widely used therapy modalities in gastric cancer include chemotherapeutic agents containing platinum such as cisplatin, carboplatin and oxaliplatin. p53 overexpression is related with platinum resistance (Lin and Howell, 2006). Reactivation of p53 is a newly searched strategy of therapy. It has been demonstrated that p53 can reactivate by Inauhzin - an enzyme inhibitor of SIRT1 that is from a family of NAD+-dependent class III histone deacetylases achieving deacetylation of p53 in tumors (Lain et al., 2008; Zhang et al., 2013). Tissue culture studies in gastric cancer have demonstrated that gene therapies targeting to decrease overexpression of p53 increase the sensitivity to radiotherapy and chemotherappy (Liu et al., 2013). Platin-free combinations such as dosataxel epirubicin combination can be used in tumors with overexpression of p53 (Nguyen et al., 2006; Roy et al., 2012).

In conclusion, in this meta-analysis we demonstrated that abnormal overexpression of immunohisochemically detected p53 is related with poor prognosis in gastric cancer. Detecting p53 expression by immunohistochemistry in patients with gastric cancer may be helpful in deciding intensity of the therapies. Therapy modalities such as gene transfer method intending to re-regulate p53 expression and p53 activators may be a hope for gastric cancer known as a progressive disease.

Acknowledgements

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