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THE PROGNOSTIC ROLE OF ERCC1 IN ADVANCED NON-SMALL CELL LUNG CANCER: A SYSTEMATIC REVIEW & META-ANALYSIS

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Abstract

Background—Observational studies have demonstrated an association between ERCC1 expression level and health outcomes in patients with advanced non-small cell lung cancer (NSCLC) treated with platinum-based regimens. This analysis presents pooled estimates of association from these studies to better elucidate the prognostic role of ERCC1 in advanced NSCLC.

Methods—A systematic literature search was conducted using the MEDLINE, EMBASE, and ASCO annual meeting databases from June, 1995 to December, 2010. Included studies were evaluated for clinical, methodological, and statistical heterogeneity. Pooled analyses were conducted using fixed and random effects models.

Results—In high ERCC1 expression vs. low ERCC1 expression patients, pooled analysis results demonstrated a significantly lower response (RR: 0.80, 0.66–0.98) and significantly higher risk of death (HR: 2.03, 1.49–2.78), respectively. Sub-group analyses demonstrated significant heterogeneity in outcomes by ERCC1 measurement method (I^2: 90.7%, p=0.001) and patient population ethnicity (I^2: 66%, p=0.003).

Conclusion—This study's findings support the hypothesis that ERCC1 expression is associated with response rate and overall survival in advanced NSCLC patients treated with platinum-based chemotherapy. Heterogeneity in sub-group analyses demonstrates the need for standardized methods to classify ERCC1 expression level, studies evaluating the association between ERCC1 expression and overall survival in non-Asian populations, and studies evaluating interaction between ERCC1 and other known prognostic factors in advanced NSCLC.

Keywords

ERCC1; advanced lung cancer; non-small cell lung cancer; prognostic; meta-analysis

Background

Lung cancer is the currently the most common cancer in the United States, with an estimated 222,000 new cases diagnosed in 2010. (1) The disease's high incidence and mortality rates

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make it the leading cause of cancer-related death in the United States, with an estimated 157,000 deaths in 2010. (1) Lung cancer consists of two primary types, non-small cell lung cancer (NSCLC) and small cell lung cancer, with NSCLC comprising approximately 80% of cases.(2) Because of the asymptomatic nature of the disease and lack of standard screening modalities to detect NSCLC at early stages, approximately 65% of cases are diagnosed at an advanced stage.(3)

Patients diagnosed with advanced non-small lung cancer (NSCLC) have poor life expectancy and few effective treatment options. (4,5) Potentially curative surgery is not a treatment option in this patient population, and so standard treatment involves platinum-based chemotherapeutic regimens with cisplatin or carboplatin.(6,7) While this treatment approach has been demonstrated to extend overall and progression free survival, these increases in survival are, on average, no more than several weeks to several months. (4,5) Additionally, research has demonstrated that a substantial proportion of advanced NSCLC patients do not respond to standard platinum-based regimens. (4) Because of the limited effectiveness of standard regimens, substantial research efforts have been undertaken to target specific agents to patient sub-groups that derive maximum benefit. (4,5) One strategy of this type is targeting platinum-based regimens based on expression levels of various DNA repair mechanisms.

DNA repair mechanisms are hypothesized to play an important role in the treatment of patients with advanced NSCLC because the presence of these factors in tumors is associated with resistance to platinum agents like cisplatin, carboplatin, and oxaliplatin. (8–10) Platinum agents exert their anti-tumor activity by binding to DNA and creating platinum–DNA adducts that can lead to cell destruction. However, this process can be inhibited when DNA repair mechanisms, such as excision repair cross-complementation group 1 (ERCC1), recognize and remove platinum-induced DNA adducts. (8–10) A prognostic association between high ERCC1 expression level and low response rates and overall survival has been established by a number of small observational studies examining advanced NSCLC patients treated with platinum-based chemotherapy. (11–21) Additionally, ERCC1 expression level has been demonstrated to have similar associations in bladder, biliary tract, pancreatic, colorectal, and ovarian cancer treated with platinum-based regimens. (22–26) To our knowledge, there has been only one prospective trial that has examined the predictive ability of an ERCC1-based strategy to select either platinum based or non-platinum based regimens in advanced NSCLC, and this study demonstrated significant increases in response in an ERCC1-guided arm versus an arm where all patients received platinum-based therapy. (27)

There has been varied use of the terms “prognostic” and “predictive” in the ERCC1 literature. We define the term “prognostic” to mean the impact of ERCC1 status on survival among patients receiving the same treatment. Therefore, a prognostic association would relate to differences in survival due to ERCC1 status, rather than differences in treatment. We define the term “predictive” to mean information about a differential treatment effect (i.e. the relative survival in the treated vs. control groups) based on ERCC1 status. Therefore, a predictive association would relate to differences in survival due to an interaction between ERCC1 status and treatment. These definitions are consistent with a number of previous reviews and analyses that have discussed the role of prognostic and predictive biomarkers in cancer outcomes. (28–34)

While ERCC1-guided treatment strategies hold great promise for enhancing the ability of physicians to “personalize” advanced NSCLC regimens, the translation of these findings into clinical practice has been limited by several factors. First, there has been only one large randomized trial examining an ERCC1-based strategy in advanced NSCLC, and many stakeholders expect more robust prospective evidence before clinical implementation. (27)

Second, because most studies to date have involved small sample sizes, many have lacked power to detect small to moderate differences in response rates or overall survival based on ERCC1 status. (11,15–18, 20–21) Third, the ERCC1 studies that have been conducted have utilized varied methods to ascertain ERCC1 levels, with some using real-time polymerase chain reaction (RT-PCR), and others using immunohistochemistry (IHC). As a result of this variation in methods, there is uncertainty about whether the ERCC1 expression level classifications of each approach are associated with equivalent health outcomes. Lastly, the majority of ERCC1 studies have been conducted in Asian populations. These populations have fundamentally different prognosis relative to alternative racial/ethnic populations, and this can limit the generalizability of the findings to other patient populations. For example, in Japanese and U.S. NSCLC patient populations, Gandara and colleagues have demonstrated different distributions of ERCC1 and other markers, as well as different health outcomes in patients treated with the same chemotherapy regimen. (35) As a result of all of these factors, considerable uncertainty remains about the association between ERCC1 status and treatment response and overall survival. To help address this uncertainty, we performed a systematic review and meta-analysis to evaluate the scientific evidence for the prognostic association between ERCC1 expression level and treatment outcomes in advanced NSCLC patients.

Materials & Methods

Literature Search Strategy

MEDLINE and EMBASE electronic databases were searched using the broad search terms: “ERCC1” and “Lung” to identify potential studies for inclusion in the analysis. Additionally, a computerized search of abstracts presented at the Annual Meetings of the American Society of Clinical Oncology (ASCO) was performed. The references in all reviewed articles were screened to identify additional articles that were not identified in the literature search described above. The time frame for all searches was June, 1995 to December, 2010. Only publications reporting results in English were evaluated for inclusion in the analysis.

Selection Criteria

This meta-analysis includes publications from studies meeting the following criteria: 1) patients had a diagnosis of advanced NSCLC, 2) all patients received platinum-based chemotherapy, 3) results are presented stratified by ERCC1 expression level, 4) the results are part of an original analysis.

Several of the studies identified using the inclusion criteria above were updates of earlier publications, and involved the same patient population. In such cases, only the most recent publication results were included in the analysis.

Data Extraction

Data were manually extracted from each publication using a data extraction form developed in Microsoft Excel (Redmond, WA, 2008). The following information was recorded for each publication: first author’s name, publication date, country of study, total number of patients in the study sample, proportion male, number of ERCC1 “high” expression patients, number of ERCC1 “low” expression patients, method used to ascertain ERCC1 expression level, covariates utilized in multivariate analyses of overall survival, proportion chemotherapy naïve at baseline, proportion with Stage IV disease, and proportion with ECOG performance status of 0. In cases where information was not presented, the article’s corresponding author was contacted to obtain the information. In the event that the given information was still not made available, it was classified as “not reported”.

Statistical Methods

The endpoints considered in the pooled analyses were response rate and overall survival. RECIST criteria were utilized to define response, with “complete response” or “partial response” classified as “response”, and “stable” or “progressive” disease classified as “non-response”. The risk ratio (RR) was abstracted or calculated to quantitatively evaluate the association between ERCC1 expression level and response rate. The association between ERCC1 level and overall survival was evaluated using the hazard ratio (HR) and 95% confidence interval from multivariate Cox proportional hazards models. In instances where the HR 95% confidence interval was not reported, the interval was derived using the reported HR and p value.

The pooled RR, HR, and 95% confidence intervals (CI) were calculated. Analyses were weighted by inverse variance. In the analysis of the association between ERCC1 level and response rate, an RR of 1 indicates a lack of association, an RR greater than 1 indicates greater response in high ERCC1 patients, and an RR less than 1 indicates greater response in low ERCC1 patients. In the analysis of the association between ERCC1 level and overall survival, a HR of 1 indicates a lack of association between ERCC1 level and risk of death, a HR of greater than 1 indicates a greater risk of death in high ERCC1 patients, and a HR less than 1 indicates a greater risk of death in low ERCC1 level patients.

The pooled RR and HR estimates were initially calculated using a fixed effects model. If the fixed effects p value for the I^2 statistic was less than 0.10, indicating significant heterogeneity across studies, the pooled estimate was calculated using a random effects model. Additionally, in instances where there was qualitative evidence of methodological heterogeneity across studies (e.g. different ERCC1 expression ascertainment methods), a random effects model was utilized.

In the sub-group analysis of ERCC1 expression ascertainment method, studies were classified as either using RT-PCR or IHC, as reported in the given publication. In the sub-group analysis of patient population type, studies conducted in Korea, China, and Japan were classified as “Asian population” and studies conducted in Spain, Denmark, Germany, Switzerland, and England were classified as “European population”.

All statistical analyses were carried out using RevMan 5.0 software (Copenhagen, Denmark, 2008).

Results

Study Characteristics

The MEDLINE electronic database search using the search terms “ERCC1” and “lung” identified a total of 220 studies. An EMBASE search did not reveal any additional studies. Searches of the ASCO meeting abstracts database (1995–2010) identified 15 abstracts, but all were early reports of studies identified through the MEDLINE and EMBASE searches. After exclusion of the studies that did not meet the inclusion criteria, 11 studies remained for analysis. Additional information about this search strategy is illustrated in flowchart form in Figure 1.

Of the 11 total studies identified through the search strategy, 9 were included in the pooled analyses of the association between ERCC1 level and response rate, and 8 were included in the analysis of association between ERCC1 level and overall survival. Table 1 lists the studies identified, their critical characteristics, and the specific analyses in which they were included. Sample sizes in the included studies ranged from 40 to 264.

Clinical and Methodological heterogeneity

The included studies varied in their approaches, with some utilizing retrospective observational designs, and other utilizing prospective observational designs. The included studies also varied in ways that could affect response rate or overall survival, including: racial/ethnic composition of the study sample, proportion with previous exposure to therapy, proportion of patients with stage IV disease, proportion of patients with different performance status levels, and proportion male. In addition, studies varied in terms of the testing methods and cutoff criteria employed to characterize ERCC1 expression levels as either “high” or “low”, with 6 utilizing RT-PCR and 5 utilizing IHC. Due to these factors, there was considerable clinical and methodological heterogeneity between studies. Consequently, random effects models were utilized to pool study results in all analyses reported below.

Statistical Pooling

The results of the pooled analysis of the association between ERCC1 level and response rate are provided in Figure 2. Though the I^2 statistic in the fixed effects model did not demonstrate significant heterogeneity in the results (I^2: 13%, p=0.33), a random effects model was utilized to pool the risk ratios due to evidence of methodological heterogeneity across studies. As Figure 2 demonstrates, patients with high ERCC1 expression levels were 20% less likely to experience response relative to patients with low ERCC1 expression levels (RR: 0.80, 95% CI: 0.66–0.98). These results indicated a statistically significant difference in response between high and low ERCC1 expression patients.

The results of the pooled analysis of the association between ERCC1 level and overall survival are provided in Figure 3. Because the I^2 statistic in the fixed effects model demonstrated statistically significant heterogeneity in the results (I^2: 70%, p=0.02), a random effects model was utilized to pool the hazard ratios for the included studies. As Figure 3 demonstrates, patients with high ERCC1 expression levels had a risk of death 2.03 times greater than patients with low ERCC1 expression levels (HR: 2.03, 95% CI: 1.49, 2.78). These results indicated a statistically significant difference in overall survival between high and low ERCC1 expression patients. The pooled hazard ratios were derived from multivariate Cox proportional hazards models that adjusted for potential confounders. While many of the covariates included in these models were the same across studies (e.g. age, gender, performance status, stage, histology), some studies adjusted for factors that were not included in other analyses (e.g. IIIβ tubulin expression, pleural effusion, BCRP expression). This finding also supports use of random effects models to pool study results.

The results of the ERCC1 ascertainment method sub-group analysis are provided in Figure 4. Because the overall I^2 statistic in the fixed effects model demonstrated statistically significant heterogeneity in the results (I^2: 70%, p=0.02), a random effects model was utilized to pool the sub-group hazard ratios. As Figure 3 demonstrates, in the RT-PCR sub-group, patients with high ERCC1 expression levels had a risk of death 3.02 times greater than patients with low ERCC1 expression levels (HR: 3.02, 95% CI: 1.96, 4.63). These results indicated a statistically significant difference in overall survival between high and low ERCC1 expression patients. Within the RT-PCR sub-group, there was very little heterogeneity in outcome (I^2: 0%, p=0.55). In the IHC sub-group, patients with high ERCC1 expression levels had a risk of death 1.63 times greater than patients with low ERCC1 expression levels (HR: 1.63, 95% CI: 1.20, 2.21). These results indicated a statistically significant difference in overall survival between high and low ERCC1 expression patients. Within the IHC sub-group, there was significant heterogeneity in outcome (I^2: 59%, p=0.04). Overall, the sub-group analysis demonstrated significant heterogeneity between the outcomes of the RT-PCR and IHC sub-groups (I^2: 90.7%, p=0.001).

The results of the patient population sub-group analysis are provided in Figure 5. Because the overall I^2 statistic in the fixed effects model demonstrated statistically significant heterogeneity in the results (I^2: 70%, p=0.02), a random effects model was utilized to pool the sub-group hazard ratios. As Figure 5 demonstrates, in the Asian population sub-group, patients with high ERCC1 expression levels had a risk of death 2.16 times greater than patients with low ERCC1 expression levels (HR: 2.16, 95% CI: 1.59, 2.95). These results indicated a statistically significant difference in overall survival between high and low ERCC1 expression patients. Within the Asian population subgroup, there was significant heterogeneity in outcome (I^2: 48%, p=0.07). In the European population sub-group, patients with high ERCC1 expression levels had a risk of death 1.8 times greater than patients with low ERCC1 expression levels (HR: 1.8, 95% CI: 0.75, 4.35). These results did not indicate a statistically significant difference in overall survival between high and low ERCC1 expression patients. Within the European population sub-group, there was significant heterogeneity in outcome (I^2: 78%, p=0.03). Overall, the sub-group analysis demonstrated significant heterogeneity between the outcomes of the Asian and European population sub-groups (I^2: 66%, p=0.003).

Publication Bias

The funnel plot for the overall pooled analysis of the association between ERCC1 level and response (Figure 6) revealed little evidence of publication bias, with a symmetrical distribution of study results around the pooled measurement of effect. Alternatively, the funnel plot for the overall pooled analysis of the association between ERCC1 level and overall survival (Figure 7) revealed an absence of studies in the lower left quadrant of the graph, where we would expect to find studies with smaller effect sizes and wider 95% confidence intervals. This finding indicated potential publication bias in favor of more positive studies. The evaluation of publication bias using the funnel plot approach was somewhat limited by the small number of studies identified for inclusion in the pooled analyses.

Discussion

The results of this systematic review and meta-analysis demonstrate the prognostic significance of ERCC1 expression level in advanced NSCLC patients with platinum-based chemotherapy. In the overall pooled analysis of the association between ERCC1 level and response, the results indicated a statistically significant increase in response in patients with low ERCC1 expression relative to patients with high ERCC1 expression. Additionally, the overall pooled analysis of the association between ERCC1 level and overall survival demonstrated statistically significant increases in overall survival in patients with low ERCC1 expression relative to patients with high ERCC1 expression. Collectively, these findings support the hypothesis that ERCC1 plays an important prognostic role in the health outcomes of advanced NSCLC patients receiving platinum-based chemotherapy. (27)

Sub-group analysis quantitatively supported the hypothesis that the strength of association between ERCC1 level and overall survival can vary based on the method utilized to ascertain ERCC1 status. While both the RT-PCR and IHC sub-groups demonstrated statistically significant associations between ERCC1 status and overall survival, the test of heterogeneity in outcome between sub-groups was statistically significant. Additionally, there was evidence of significant heterogeneity between studies in the IHC group (I^2=62%, p=0.03), but results were very consistent in the RT-PCR subgroup (I^2=0% p=0.40). This finding suggests that the methods and cut-points in studies utilizing RT-PCR may be more consistent than those in studies utilizing IHC. Issues surrounding the comparability of RT-PCR and IHC results have been discussed in greater detail by Vilmar and Sorenson. (36)

Overall, the heterogeneity demonstrated in this subgroup analysis emphasizes the need for standardized methods and cut points to classify ERCC1 expression level as “high” or “low”.

Sub-group analyses also demonstrated that the strength of association between ERCC1 status and overall survival varies between populations of Asian and European descent. This effect was demonstrated by the significant heterogeneity in outcome between Asian and European sub-groups. It is unclear if this heterogeneity is the result of a true underlying biological effect, or merely the result of the small number of studies that have been conducted in European populations. While several studies have demonstrated favorable NSCLC prognostic factors in Asian patients relative to Caucasian patients (e.g. never-smokers, EGFR status, adenocarcinoma histology), it remains unclear if these factors impact ERCC1-based health outcomes. (35,37,38) Our study-level data did not allow us to evaluate these types of relationships, but this is an interesting area for future research. For example, Gandara and colleagues recently demonstrated an association between ERCC1 status and EGFR status, however this study was unable to evaluate the impact of this association on health outcomes due to data limitations. (39) Overall, the findings of this sub-group analysis emphasize the need for additional study of the association between ERCC1 status and overall survival in non-Asian populations, as well as interactions between prognostic factors in the general NSCLC population.

While the response rate pooled analysis showed little evidence of publication bias, the overall survival analysis did demonstrate some evidence of publication bias. The overall survival funnel plot lacked studies in the lower left quadrant, demonstrating a lack of studies with smaller effect sizes and greater variability, and indicating bias in favor of more positive outcomes. Inclusion of studies in the lower left quadrant would be expected to decrease the strength of association between low ERCC1 status and prolonged survival. However, because these studies would be expected to have very small sample sizes and high variability, they would contribute very little weight to the pooled analyses. Consequently, the association between ERCC1 status and overall survival would be likely to remain statistically significant, and relatively strong, even if such studies were included in the overall survival analysis. This suggests that the association between ERCC1 status and overall survival demonstrated by this study should be robust to any potential publication bias.

This analysis only addresses the prognostic significance of ERCC1 expression because there is a lack of studies examining the predictive role of this biomarker. No studies to date have investigated ERCC1 expression testing as a predictive means to select advanced NSCLC patients for platinum-based chemotherapy with the intention of improving survival. Cobo et al. conducted the only predictive ERCC1 study identified by the search strategy outlined above, but this study was not included in the pooled analyses because high ERCC1 patients did not receive platinum-based chemotherapy. In that study, patients were randomized to either a standard care arm that received platinum-doublet therapy (cisplatin/docetaxel), or an ERCC1-guided arm where patients with high ERCC1 received non-platinum therapy (gemcitabine/docetaxel) and patients with low ERCC1 received platinum-doublet therapy (cisplatin/docetaxel). (27) The primary outcome was objective response rate. The results of this study demonstrated statistically significant increases in response in the ERCC1-guided arm relative to the standard care arm (59.2% vs. 39.3%, p=0.03). (18) The study also examined secondary endpoints for progression-free survival (PFS) and overall survival (OS), but demonstrated a non-significant protective effect in the ERCC1-guided arm (PFS HR: 0.9, 0.7 to 1.1; OS HR: 0.9, 0.7 to 1.2). (27) This study serves as an example of a prospective design that could be used to investigate the role of an ERCC1-guided treatment strategy in advanced NSCLC. However, future studies of this type should focus on overall survival, as this is the outcome that is likely most relevant to patients and medical decision-

makers. It should also be noted that studies in early-stage NSCLC, as well as bladder, biliary tract, pancreatic, colorectal, and ovarian cancer, suggest there may be a prognostic and/or predictive role for ERCC1 status and treatment with platinum-based chemotherapy. (22–26,40)

There has been only one other meta-analysis of the association between ERCC1 expression and health outcomes in advanced NSCLC patients undergoing platinum-based chemotherapy. This study was conducted by Chen et al. in 2010, and demonstrated an association between low ERCC1 expression levels and increased odds of response (OR: 0.48, 0.35 to 0.64), as well as a more favorable median overall survival ratio (MR: 0.77, 0.47 to 1.07). (41) Additionally, Chen et al. conducted sub-group analyses by ERCC1 ascertainment method, and found that there was not statistically significant differences between RT-PCR and IHC subgroups in measuring the strength of association between ERCC1 status and response rate (I^2: 0%, p=0.57). (41) While many of the findings of the Chen et al. study are concordant with the findings of this meta-analysis, there are several methodological factors that this study seeks to improve upon. Chiefly, in the pooled analysis of overall survival, the Chen et al. study utilized median overall survival ratios, which have been demonstrated to be problematic in pooled analyses. (42) Michiels et al. illustrated the problems with using median ratios as a surrogate marker for time-to-event outcomes in a 2005 publication comparing the ability of median ratios, odds ratios, and hazard ratios to represent patient-level outcomes. (42) Additionally, Chen et al. did not clearly define their methods for pooling the median survival ratios, and did not assess heterogeneity in that analysis. Also, in the Chen et al. pooled analysis of objective response rate, a pooled odds ratio was presented even though response fails to meet the rare disease assumption, and is not likely to approximate the risk ratio. For example, in this analysis, we calculated a pooled risk ratio of 0.80 (0.66, 0.98), whereas a pooled analysis of the same studies yields an odds ratio of 0.69 (0.51, 0.91). Additionally, the Chen et al. analysis of response rate utilized a fixed effects model despite evidence of significant heterogeneity between studies according to commonly accepted meta-analysis practices (I^2=45%, p=0.05). (43) Lastly, the Chen et al. analysis did not include a number of studies that have been recently published. This analysis seeks to overcome these issues by pooling hazard ratios to evaluate the association between ERCC1 status and overall survival, utilizing random effects models to pool outcomes in the presence of significant heterogeneity, and including studies published through December of 2010.

This study had a number of limitations that are worth noting. First, this analysis was performed at the study level, which limited ability to explore the potential for confounding by various demographic and clinical factors (e.g. ethnicity, gender, smoking status, and histology). Second, this study was predominately based on the findings of observational studies, which inherently contain greater potential for confounding than randomized controlled trials. Lastly, because the vast majority of studies included in the pooled analyses of overall survival were carried out in Asian populations, it is possible that the results of these analyses are not readily generalizable to other populations.

Collectively, this study's overall findings support the hypothesis that ERCC1 expression level is associated with both response and overall survival in advanced NSCLC treated with platinum-based regimens. Future studies should seek to extend these findings to include prediction of platinum-based chemotherapy benefit in terms of both progression-free and overall survival. Additional studies are required in this area before ERCC1 testing can move toward routine clinical application as a predictive and prognostic tool in advanced non-small cell lung cancer.

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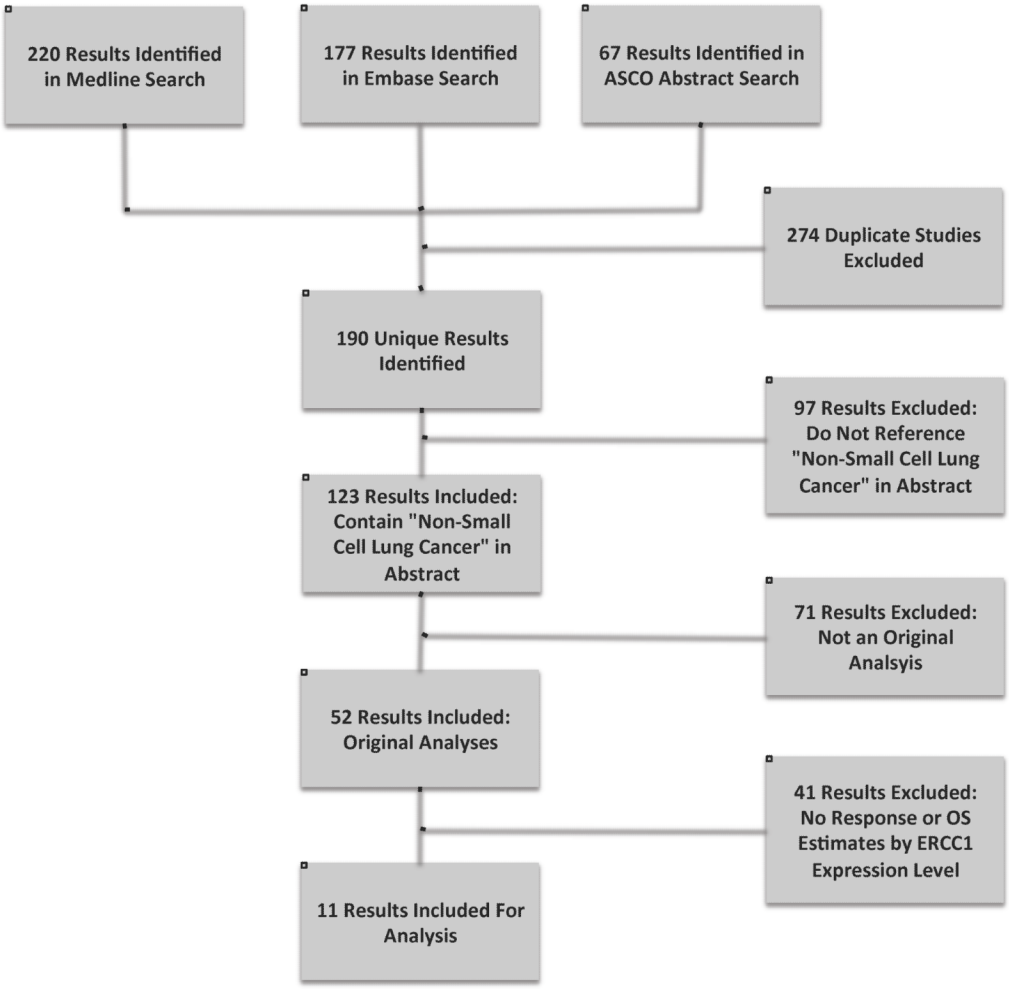

Figure 1. Electronic Search Flow Chart

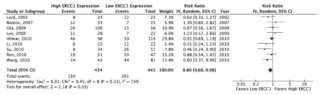

Figure 2. ERCC1 Expression and Response Rate Pooled Analysis Results

This figure presents the study-level results and pooled analysis results for the association between ERCC1 status and response. The pooled analysis demonstrates a RR=0.80 (95% CI: 0.66, 0.98), significantly favoring low ERCC1 patients.

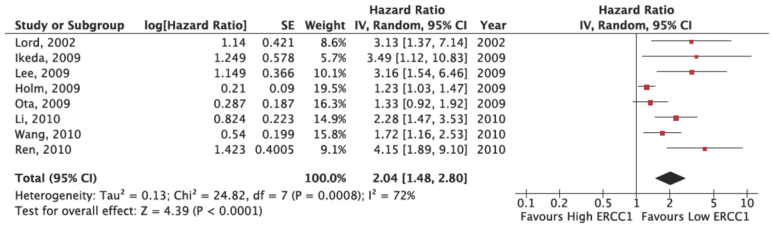

Figure 3. ERCC1 Expression and Overall Survival Pooled Analysis Results

This figure presents the study-level results and pooled analysis results for the association between ERCC1 status and overall survival. The pooled analysis demonstrates a HR=2.04 (95% CI: 1.48, 2.80), significantly favoring low ERCC1 patients.

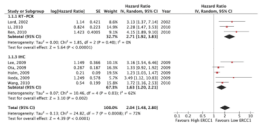

Figure 4. ERCC1 Expression and Overall Survival Ascertainment Method SubGroup Pooled Analysis Results

This figure presents the study-level results and pooled analysis results for the association between ERCC1 status and overall survival by ascertainment method sub-group. The RT-PCR sub-group pooled analysis demonstrates a HR=2.71 (95% CI: 1.92, 3.83), significantly favoring low ERCC1 patients. The IHC subgroup pooled analysis demonstrates a HR=1.63 (95% CI: 1.20, 2.21), and also significantly favors low ERCC1 patients. There is evidence of significant heterogeneity within the IHC sub-group (I^2=62%, p=0.03), as well as between sub-groups (I^2=72%, p=0.0008).

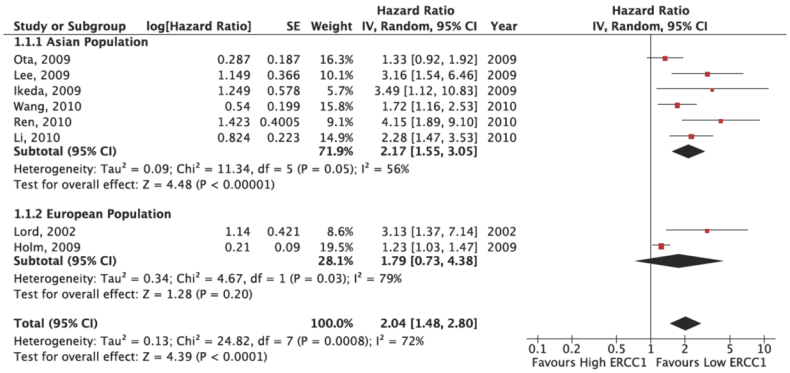

Figure 5. ERCC1 Expression and Overall Survival Population Sub-Group Pooled Analysis Results

This figure presents the study-level results and pooled analysis results for the association between ERCC1 status and overall survival by population sub-group. The Asian population sub-group pooled analysis demonstrates a HR=2.17 (95% CI: 1.55, 3.05), significantly favoring low ERCC1 patients. The European population sub-group pooled analysis demonstrates a HR=1.79 (95% CI: 0.73, 4.38), favoring low ERCC1 patients, but with non-significant results. There is evidence of significant heterogeneity within the Asian (I^2=56%, p=0.05) and European (I^2=79%, p=0.03) sub-groups, as well as between sub-groups (I^2=72%, p=0.0008).

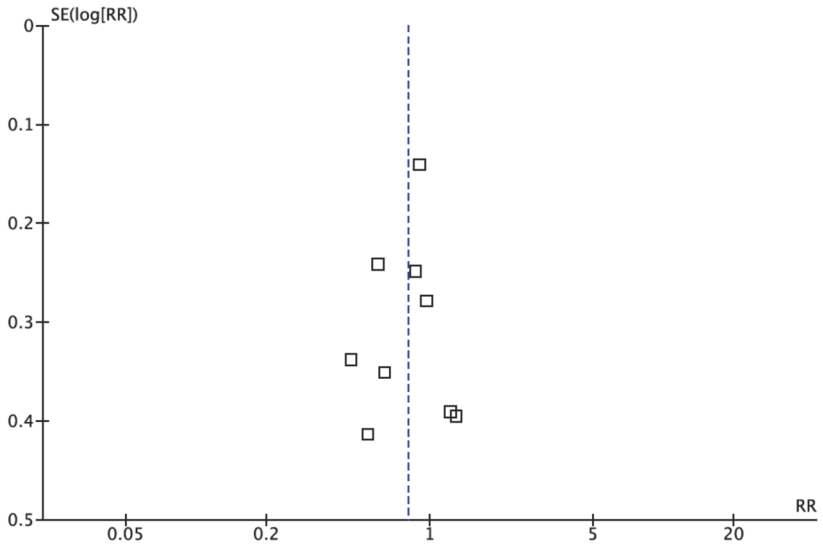

Figure 6. Publication Bias Funnel Plot for ERCC1 Expression and Response Rate Random Effects Pooled Analysis

This figure demonstrates little evidence of publication bias based on its symmetrical distribution of study results around the pooled effect estimate.

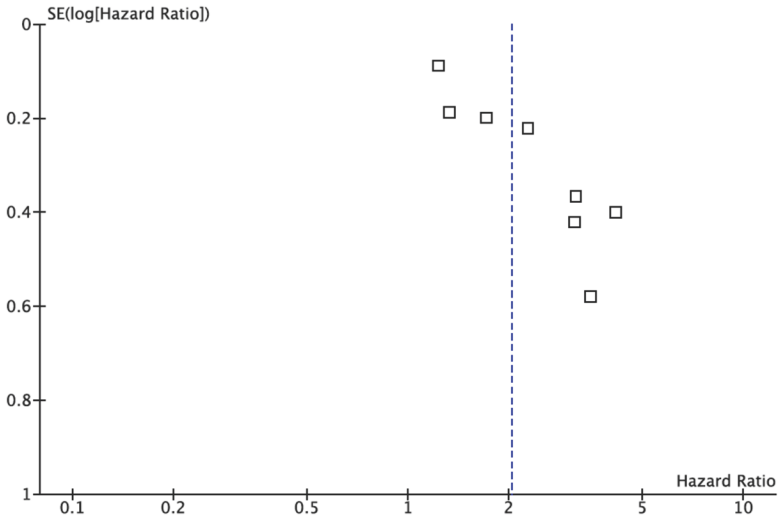

Figure 7. Publication Bias Funnel Plot for ERCC1 Expression and Overall Survival Random Effects Pooled Analysis

This figure demonstrates evidence of publication bias based on its lack of studies in its lower left quadrant, where we would expect to find studies with smaller effect sizes and greater levels of variability.

Table 1

Studies Included in Pooled Analyses

This table provides the key characteristics of the studies included in this meta-analysis, as well as the specific analyses to which each study contributed.

First Author	Year	Population	Patients	ERCC1 Measurement Method	Response Rate Pooled Analysis	Overall Surviva Pooled Analysis
Ren[11]	2010	Asian	100	RT-PCR	X	X
Su[12]	2010	Asian	85	RT-PCR	X	
Wang[13]	2010	Asian	124	IHC	X	X
Ikeda[14]	2009	Asian	40	IHC		X
Lee[15]	2009	Asian	50	IHC	X	X
Lord[16]	2002	European	56	RT-PCR	X	X
Ota[17]	2009	Asian	156	IHC	X	X
Booton[18]	2007	European	66	RT-PCR	X	
Holm[19]	2009	European	163	IHC		X
Li[20]	2010	Asian	115	RT-PCR	X	X
Vilmar[21]	2010	European	264	IHC	X	

Table 2
Studies Included in the ERCC1 Expression and Response Pooled Analysis

This table provides response rates by ERCC1 status for each study included in the pooled analysis of response.

First Author	Year	% Response Low ERCC1	% Response High ERCC1
Ren[11]	2010	42.6%	37.3%
Su[12]	2010	51.9%	23.5%
Wang[13]	2010	54.3%	32.6%
Lee[15]	2009	32.0%	39.0%
Lord[16]	2002	52.0%	36.4%
Ota[17]	2009	27.0%	26.0%
Booton[18]	2007	28.0%	36.4%
Li[20]	2010	47.8%	26.1%
Vilmar[21]	2010	51.8%	46.9%

* Response by RECIST criteria

Table 3
Studies Included in the ERCC1 Expression and Overall Survival Pooled Analysis

This table provides the covariates included in the cox proportional hazards models for each study included in the overall survival pooled analyses and sub-group analyses.

First Author	Year	Cox Proportional Hazard Model Covariates
Ren[11]	2010	Age, Gender, Stage, Histology, PS, Smoking, Response
Wang[13]	2010	Age, Gender, Histology, PS, Pleural Effusion, Metastatic Sites
Ikeda[14]	2009	Age, Gender, Stage, Histology, IIIB Tubulin
Lee[15]	2009	Smoking, Histology, PS, Response
Lord[16]	2002	Age, Gender, Stage, Histology, PS, Weight Loss
Ota[17]	2009	Age, Gender, Histology, PS, Smoking, BCRP
Holm[19]	2009	Age, Gender, Histology
Li[20]	2010	Response, MRP1, LRP

PS=Performance Status