

The prognostic value of excision repair cross-complementing Group 1 expression in nasopharyngeal cancer patients

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Background: Overexpression of excision repair cross-complementing Group 1 (ERCC-1) is related to cisplatin resistance and defective repair of radiation damage. The purpose of this study was to evaluate the clinical significance of excision (ERCC-1) expression in nasopharyngeal cancer (NPC). **Materials and Methods:** We conducted a retrospective review of patients diagnosed with NPC between 2000 and 2013. The archived tissues were analyzed using immunohistochemistry to determine ERCC-1 expression. The ERCC-1 expression level along with other clinical factors and overall survival (OS) were analyzed. Hazard ratio (HR) with a 95% confidence interval was calculated to assess the risk. **Results:** The analysis of ERCC-1 expression was available in 262 NPC patients who had medical records at our hospital. Among those patients, 221 (84%) were treated with curative radiotherapy (RT)/concurrent chemoradiotherapy, 22 (7%) were treated with palliative RT alone, and 19 (9%) were given best supportive care. There was no correlation between ERCC-1 expression and stage of cancer or OS. No difference in 5-year OS was found between patients with low ERCC-1 expression and high ERCC-1 expression (38% vs. 36%; $P = 0.981$). The adjusted HR (aHR) of cancer death increased with cancer stage (aHR = 2.93 for advanced Stages III–IV; $P = 0.001$) and age (aHR = 2.11 for age >55; $P \leq 0.001$). ERCC-1 expression exhibited no prognostic significance in our study (aHR = 1). **Conclusion:** In this study, ERCC-1 expression has no statistical significance to be considered a prognostic factor for OS among NPC patients. On the other hand, cancer stage, age, and types of treatment can be prognostic factors in NPC patients.

Key words: Excision repair cross-complementing Group 1, nasopharyngeal cancer, prognostic factor

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INTRODUCTION

The incidence rate of nasopharyngeal cancer (NPC) is high in Southeastern Asia, in both sexes, with the disease being the sixth most common among males in this region.^[1] In Thailand, the age-standardized incidence rates of NPC are approximately 2.8 and 0.9 per 100,000 in males and females, respectively.^[2] Chiang Mai, a province in the Northern part of Thailand, has an incidence

rate of 2.7 for males and 1.2 for females.^[2] Due to anatomical location and extension of disease, as well as a high degree of radiosensitivity, the standard treatment for NPC is definitive radiotherapy (RT) with or without chemotherapy, depending on the stage of the disease. Although the latest evidence has shown a significant improvement in survival with the addition of concurrent platinum-based chemotherapy, a cornerstone chemotherapy regimen, to RT in locoregionally advanced NPC,^[3] the treatment outcomes for this group of patients are rather

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unsatisfactory with the 5-year overall survival (OS) rates of 53%–80% in Stage III and 28%–61% for Stage IV.^[4-9]

Many studies have suggested a potential use of excision repair cross-complementation Group 1 enzyme (ERCC-1) as a molecular predictor of the treatment outcome of platinum-based chemoradiotherapy in NPC.^[10-14] ERCC-1 is an important enzyme in the nucleotide excision repair (NER) pathway which is involved in the DNA repair mechanism in tumor cells damaged by treatment with platinum agents. A study of ERCC-1 in head-and-neck cancer patients treated with RT alone has shown that the high expression of ERCC-1 was associated with poor response to RT, thereby having a role in the repair of RT-induced DNA damage.^[15] The objective of this study was to evaluate the clinical significance including treatment outcomes of ERCC-1 expression in NPC patients.

MATERIALS AND METHODS

We considered 382 archived NPC specimens from patients diagnosed between January 2000 and December 2013 at the Faculty of Medicine, Chiang Mai University. The inclusion criteria were having biopsy-proven NPC, having adequate information on staging and treatment, and having archive tissues available for ERCC-1 immunohistochemical (IHC) staining. The data were extracted from the medical records. Among the treatment outcome determining factors and associating factors, age, sex, stage, and type of treatment were included in this study. The cancer stage was determined using the American Joint Committee on Cancer staging system.^[16-18]

According to clinical practice guidelines for nasopharyngeal cancer, Stage I disease is generally treated by RT alone, while higher nonmetastatic stages are received concurrent chemoradiotherapy (CCRT). In our center, patients who had tumors confined to the nasopharynx without lymph node involvement were given curative RT alone by two-dimensional RT, three-dimensional conformal radiotherapy, or intensity-modulated radiotherapy. Patients who have tumor extension beyond nasopharynx and/or lymph node involvement with good performance status and adequate renal, bone marrow, and liver function received CCRT plus either neoadjuvant or adjuvant platinum-based chemotherapy.

Neoadjuvant or adjuvant chemotherapy consisted of three cycles of cisplatin (100 mg/m²) or carboplatin AUC5 on day 1 plus 5-FU 1000 mg/m² on days 1–4. Concurrent chemotherapy regimen was either cisplatin 100 mg/m² every 3 weeks or weekly 40 mg/m² or weekly carboplatin 100 mg/m². Patients with advanced disease and poor performance status received either palliative RT or best supportive care.

Formalin-fixed, paraffin-embedded tissue sections were stained, using VENTANA BenchMark XT platform, with the antibody against ERCC-1 (rabbit anti-human ERCC-1 monoclonal antibody, Clone SP68, Spring Bioscience, Pleasanton, CA, USA, 1:100), and then, were visualized by the ultraView Universal DAB Detection Kit. ERCC-1 expression was assessed on digital scanned microscopic images (Aperio, Aperio Technologies Inc., Vista, CA, USA) using image analysis (ImageScope software) by a pathologist who was masked to the clinicopathological data. Only well-preserved tumor areas were selected from the whole section for the analysis. Using nuclear count V9 algorithm, the results in percentage were reported as 0 – negative; 1+ – weakly positive; 2+ – moderately positive; and 3+ – strongly positive nuclei staining [Figure 1]. As the result of 1+ nuclei could not be specifically observed at the margin of tissue or at the areas of crushing artifacts, only percentages of 2+ and 3+ nuclei were used to calculate ERCC-1 expression. Patients were then categorized into two groups: “high expression” or “low expression”, using the median as a cut point.

Statistical analysis

Data were presented as mean with standard deviation (SD) or median with interquartile range (IQR) as appropriate for continuous variables and as counts and percentages for categorical variables. The proportions of ERCC-1 high expression in categorical variables were compared using Fisher’s exact test or Chi-square test as appropriate. Student’s *t*-test was used to compare the mean age between high and low expression of ERCC-1. The time to events was measured from the time of diagnosis to the date of events, i.e., death for OS analysis. The survival rate was calculated using the Kaplan–Meier method, and the log-rank test was performed for the significance test. The association between baseline characteristics (sex, age, stage of cancer, type of treatment, and ERCC-1 expression) and events was assessed using univariable and multivariable Cox proportional hazards models. Age and ERCC-1 expression were dichotomized according to the median values. Any variable having a significant univariate test at *P* value cutoff point of below 0.25 was selected as a candidate for the multivariate analysis. All reported *P* values are two sided and *P* < 0.05 was considered statistically significant. All analyses were performed using STATA software version 10.1 (StataCorp, College Station, TX, USA). This study was approved by the Research Ethics Committee of Faculty of Medicine, Chiang Mai University.

RESULTS

Of 382 NPC patients retrieved from the database, only 262 were eligible for the present study. The consort diagram of

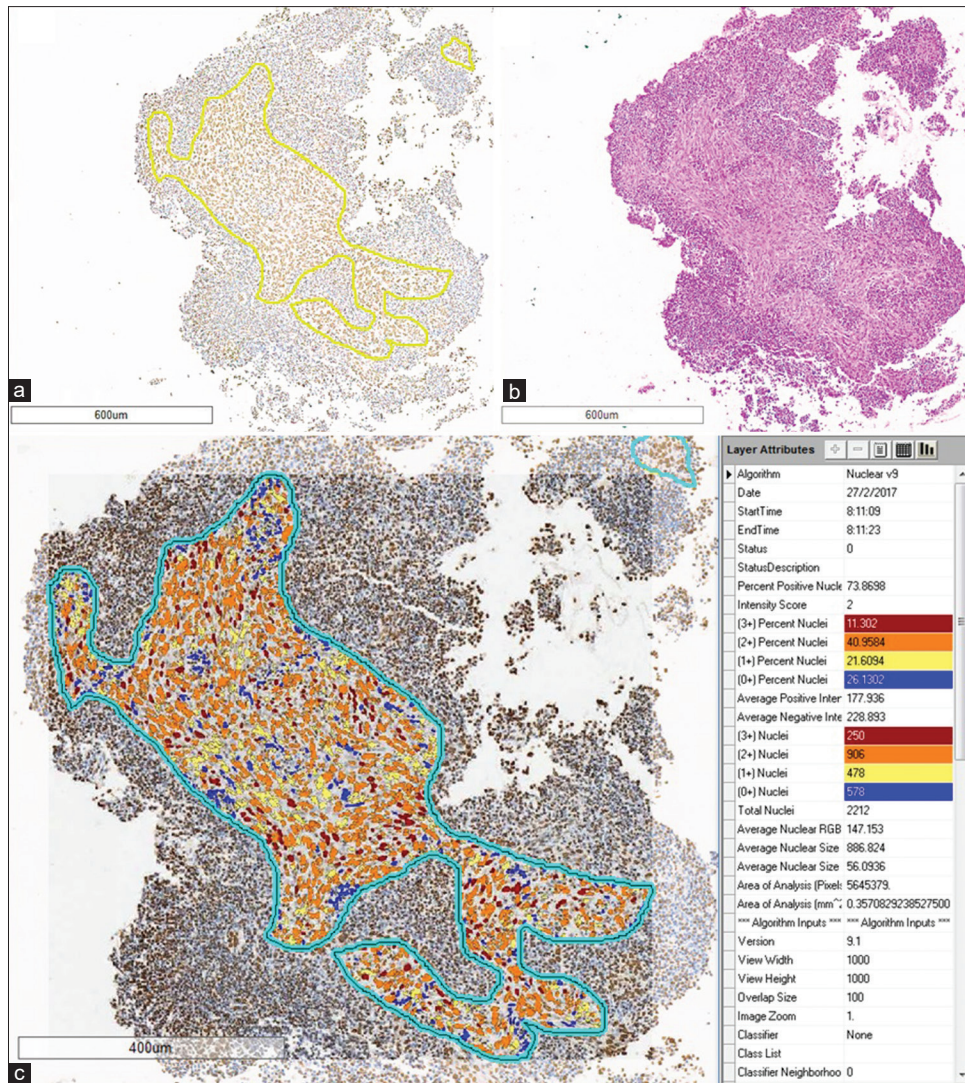


Figure 1: Image analysis for excision repair cross-complementing Group 1 expression. Tumor areas were selected from excision repair cross-complementing Group 1 immunohistochemical-stained section (a) for image analysis, guided by a H and E-stained section (b). Image analysis results were displayed as shown in panel (c). Only cells with 2+ and 3+ nuclear staining were used for the statistical analysis

the study is presented in Figure 2. Among 120 patients who were excluded from the study, eight were with squamous cell carcinoma of primary sites other than nasopharynx, 41 were due to the lack of medical records on their staging or type of treatment, and 71 were due to unavailability of archive tissues for ERCC-1 IHC staining.

The mean (SD) age of the study population was 55 years.^[13] Most were male (70%) and in advanced stages (87% in Stage III–IV). For the type of treatment, 221 patients (84%) received curative RT/CCRT, while 41 patients (16%) received either palliative RT or best supportive care. Table 1 summarizes the baseline characteristics of a patient by the level of ERCC-1 expression. One hundred and thirty-five patients (52%) had high expression of ERCC-1 and 127 patients (49%) had low expression of ERCC-1. There was no difference in any baseline characteristics between both the groups.

The median follow-up time was 2.8 years (IQR: 1.2–5.8). For 5-year survival analysis, 163 patients (62%) had died, with median OS of 33 months (IQR: 15–69). Age, stage of cancer, and type of treatment were significantly predictive of OS using univariable and multivariable Cox regression analyses [Table 2]. However, ERCC-1 expression showed no prognostic significance.

Five-year OS rates were better in age group below 55 years than in older group (47% [95% confidence interval (CI): 38–55] vs. 28% [95% CI: 20–36]; $P < 0.001$), in early Stages (I–II) than in advanced Stages (III–IV) (67% [95% CI: 48–80] vs. 33% [95% CI: 27–39]; $P < 0.001$), and in curative RT/CCRT than palliative RT/best supportive care groups (41% [95% CI: 34–48] vs. 9% [95% CI: 2–25]/21% [95% CI: 7–41]; $P < 0.001$, respectively) [Figure 3]. There was no difference in 5-year OS rate between low and high ERCC-1 expression (38% [95% CI: 30–47] vs. 36% [95% CI: 29–44]; $P = 0.98$).

Table 1: Baseline characteristics and clinicopathological factors by excision repair cross-complementing Group 1 expression

Variables	All patients (n=262), n (%)	ERCC-1		P*
		Low expression (n=127), n (%)	High expression (n=135), n (%)	
Sex				
Female	79 (30)	40 (51)	39 (49)	0.646
Male	183 (70)	87 (48)	96 (52)	
Median age (year), mean (SD)	55 (13)	55 (14)	55 (13)	0.994†
Age groups (years)				
<55	128 (49)	57 (44)	71 (56)	0.212
≥55	134 (51)	70 (52)	64 (48)	
Stage (n=258)				
I	10 (4)	4 (40)	6 (60)	0.591‡
II	24 (9)	14 (58)	10 (42)	
III	80 (31)	35 (44)	45 (56)	
IV	144 (56)	71 (49)	73 (51)	
Treatment				
Curative RT/CCRT	221 (84)	104 (47)	117 (53)	0.555
Palliative radiotherapy	22 (9)	12 (55)	10 (45)	
Best supportive care	19 (7)	11 (58)	8 (42)	

*Chi-square test; †Student's t-test; ‡Fisher's exact test. RT=Radiotherapy; CCRT=Concurrent chemoradiotherapy; CI=Confidence interval; SD=Standard deviation; ERCC-1=Excision repair cross-complementing Group 1

Table 2: Overall survival: Univariable and multivariable Cox proportional hazard regression analysis

Covariates	Univariable analysis			Multivariable analysis		
	HR	95% CI	P*	aHR	95% CI	P*
Sex						
Female	1.00			1.00		
Male	1.32	0.93-1.86	0.117	1.33	0.93-1.91	0.117
Age groups (years)						
<55	1.00			1.00		
≥55	1.83	1.34-2.51	<0.001	2.11	1.50-2.97	<0.001
Stage						
Early (I-II)	1.00			1.00		
Advanced (III-IV)	2.86	1.55-5.28	0.001	2.93	1.58-5.46	0.001
Treatment						
Curative RT/CCRT	1.00			1.00		
Palliative radiotherapy	2.82	1.75-4.54	<0.001	2.11	1.27-3.49	0.004
Best supportive care	2.86	1.68-4.90	<0.001	4.49	2.45-8.24	<0.001
ERCC-1 expression						
Low	1.00			1.00		
High	1.00	0.74-1.36	0.981	1.08	0.79-1.47	0.647

*P value from partial likelihood ratio tests. RT=Radiotherapy; CCRT=Concurrent chemoradiotherapy; CI=Confidence interval, HR=Hazard ratio; aHR=Adjusted hazard ratio

DISCUSSION

The outcome of chemoradiotherapy in locoregional advanced NPC patients is still dismal. The 5-year OS rate in this retrospective study is very poor when compared to other studies, as more than half of the patients (56%) included in our study were at Stage IV at diagnosis. Imaging study for tumor evaluation, staging, and RT treatment planning in most of our patients was by CT scanning,

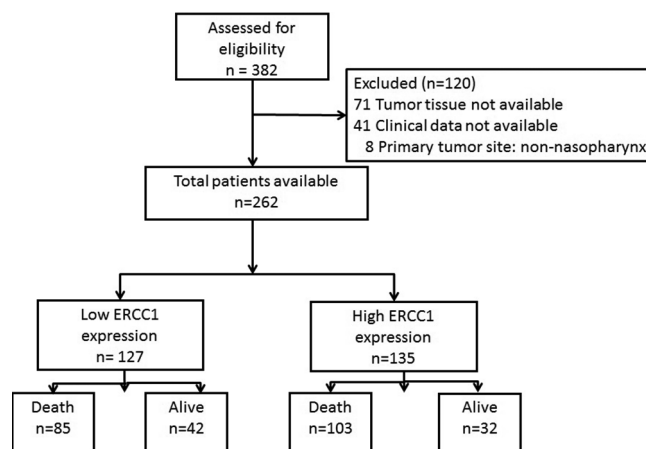


Figure 2: Consort diagram of the study

while magnetic resonance imaging is better for evaluating intracranial and skull base involvement.^[19] This may result in an underestimate of tumor stage and effect treatment decision-making, RT field, and outcomes. However, when we analyzed the OS in each stage, the outcome of the patients in this cohort was in line with other studies.^[4-9] The 5-year OS of Stage I, II, III, and IV of our patients was 80%, 62%, 42%, and 28%, respectively.

The success of this combination treatment depends on the effectiveness of lethal cell killing and double-strand break by RT and on the synergism effect of cytotoxicity by platinum-based chemotherapy. NER is one of four major pathways to repair damaged DNA.^[16] It also plays an important role in identifying and repairing the DNA adducts, particularly those induced by cisplatin.^[17] ERCC-1 has a crucial role for the incision step and completion

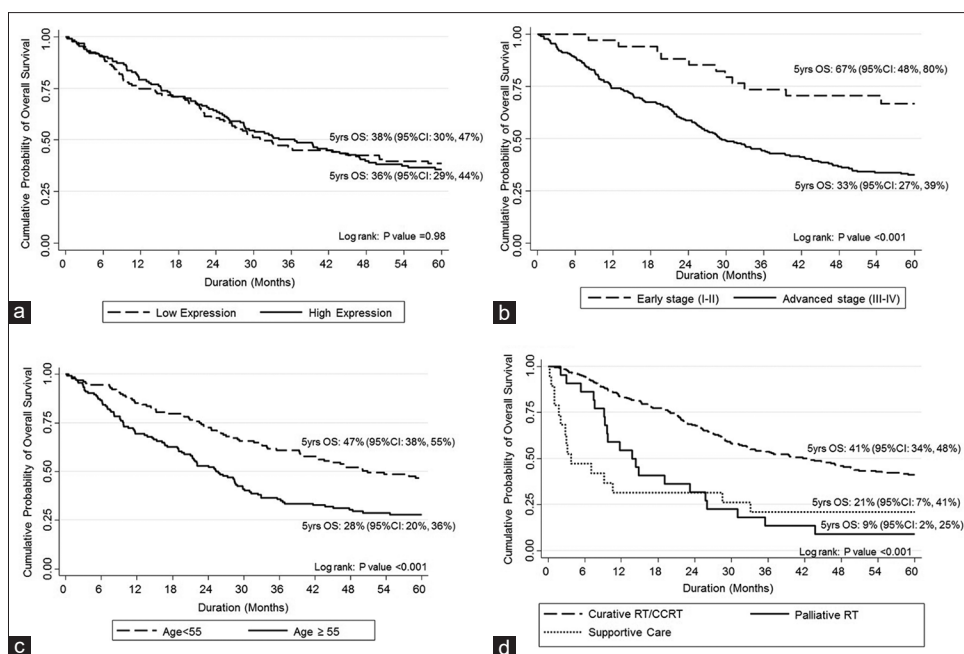


Figure 3: Kaplan–Meier curves of overall survival according to prognostic factors. There is a significant difference in 5-year overall survival between early and advanced stages (b), age group (c) and treatment (d), but not excision repair cross complementing Group 1 expression level (a)

of the NER pathway.^[19] Many studies reported ERCC-1 to be involved in the different repair mechanisms such as interstrand cross-link repair and homologous recombination repair.^[20-22] Overexpression of ERCC-1 has been found in many cancer types, and it has been proposed that ERCC-1 overexpression may serve as a prognostic and/or predictive tumor marker.^[23-28] Overexpression of ERCC-1 also predicted low sensitivity to the platinum-based regimen for many cancers.^[23-25] Results from these published data are still inconsistent.^[20-22]

The prognostic values of ERCC-1 expression have been studied in nasopharyngeal cancer studies,^[10,13,29] but the values of it remained controversial. Chan *et al.*^[10] identified that a high ERCC-1 expression predicted a two-fold increase in risk only for locoregional failure but not OS in a retrospective study of NPC. They also concluded that chemotherapy response is not affected by ERCC-1 expression. In line with Chan *et al.*,^[10] our study has not found any differences in OS between the high and low expression of ERCC-1. Even when we focused on the group of patients who received CCRT, the expression of ERCC-1 failed to demonstrate significant OS differences between high and low expression. In contrast with Xu *et al.*,^[29] they reported higher 3-year OS, failure-free survival, locoregional failure-free survival, and distant failure-free survival in the patients with ERCC-1 positive and suggested that ERCC-1 might be a predictor of response to platinum-based chemoradiotherapy. The study by Shen *et al.*^[13] also found that the overall response rate and 5-year distant recurrence risk of the patients with high expression of ERCC-1 are poorer than those of the control patients with low ERCC-1

expression. However, their study did not report on OS. In our study, we found that higher stage, age older than 55, and not receiving chemoradiotherapy were prognostic factors of poor OS but not ERCC-1 expression. We tend to agree with Hayes *et al.*^[30] for their explanations on the lack of the usefulness of ERCC-1 expression as a prognostic factor of survival, i.e., the synergism of concurrent chemotherapy and radiation is able to overcome the relative resistance to platinum conferred by ERCC-1 expression. In our study, most of the patients (80%) received CCRT with platinum based.

As shown in Table 1, we did not find any association between cancer stage and the level of ERCC-1 expression despite using an automated IHC staining platform and objective evaluation. All cases were positively stained for ERCC-1; however, an overall range of expression level was quite narrow (61%, IQR: 40–76). One limitation in the tissue study of nasopharyngeal cancer is that biopsied tissues were usually small, and the crushing artifact was not uncommonly present. This results in a reduction in tissue area for evaluation of ERCC-1 expression. However, in the present study, all well-preserved tumor areas were selected for objective digital image analysis to minimize the bias. Considering the heterogeneity of the interpretation method of ERCC-1 expression, it is difficult to compare our results to others.

CONCLUSION

ERCC-1 expression is not a prognostic factor of OS in patients with nasopharyngeal cancer. Further studies with

larger sample sizes are required to investigate whether or not ERCC-1 may use as a prognostic factor for this cancer.

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Conflicts of interest

There are no conflicts of interest.

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