

Clinical observation of gene expression-guided chemoradiation therapy for nonsurgical esophageal squamous cell carcinoma patients: a retrospective analysis of 36 cases

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Objective: To make an informed choice of chemotherapy drugs according to the oncogene mRNA expression and to explore whether it could increase the survival rate of patients.

Patients and methods: The study retrospectively analyzed 36 cases of nonsurgical esophageal squamous cell carcinoma patients treated at the Center for Oncology of Shandong Provincial Hospital from December 1, 2010, to November 1, 2013. Intensity-modulated radiation therapy was used for the treatment with a conventional radiotherapy dose of 60–66 Gy. Chemotherapy started 1–5 weeks after radiation therapy. The selection of the chemotherapy drug was based on the mRNA expression levels of excision repair cross-complementation 1, thymidylate synthetase, ribonucleotide reductase M1, and β -tubulin isotype III. The objective response rate, progression-free survival, and overall survival were observed.

Results: The reason for poor prognosis of patients with high expression of excision repair cross-complementation 1 was unknown. No correlation was observed between patient survival and expression of thymidylate synthetase, ribonucleotide reductase M1, and β -tubulin isotype III. Complete response, partial response, stable disease, and progressive disease were observed in 25, five, three, and three patients, respectively. The objective response rate was 83.3%. The 1-year, 2-year, and 3-year progression-free survival rates were 79.8%, 58.9%, and 54.4%, respectively. The 1-year, 2-year, and 3-year overall survival rates were 83.3%, 68.1%, and 58.4%, respectively.

Conclusion: Selecting the chemotherapy drug according to the oncogene expression, combined with radiation therapy, could increase the 3-year survival rate in nonsurgical esophageal squamous cell carcinoma patients. Such conclusion needs to be further confirmed using a larger sample size.

Keywords: esophageal squamous cell carcinoma, gene expression, chemoradiation therapy, survival

Introduction

Esophageal carcinoma is a popular malignant tumor in the People's Republic of China, with a high degree of malignancy and poor prognosis. Reportedly, 40%–60% of patients are not eligible for surgery due to distant metastasis or a high surgical risk.¹ Thus, radiation therapy plays a more important role, especially for locally advanced and inoperable patients.² However, the 5-year survival rate is only 10% for nonsurgical esophageal carcinoma patients using routine radiotherapy. The RTOG85-01 study confirmed that chemoradiation therapy could improve the 5-year survival rate of

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esophageal carcinoma compared with radiotherapy alone (27% vs 0%, $P < 0.0001$).³ In contrast to European and American countries, >90% of pathological types of esophageal are squamous cell carcinoma in the People's Republic of China. In 2011, Kato et al reported that cisplatin-based chemoradiation therapy, with a radiation dose of 60 Gy, could increase the 5-year survival rate to 36.8%.⁴ The study described the difference in concurrent chemotherapy tolerance in East Asians, Europeans, and Americans. For non-surgical esophageal carcinoma patients, radiation therapy combined with chemotherapy is now recognized as a standard treatment, but the best chemotherapy regimen is unclear. Regional recurrence and distant metastasis are the two major reasons for treatment failure.^{3,5} Therefore, improving the therapeutic efficacy is an urgent problem that needs to be addressed clinically.

The drugs recommended for chemoradiation therapy include cisplatin, 5-fluorouracil (5-FU)/capecitabine, and taxol/docetaxel. Studies have reported that the mRNA expression level in tumor may predict drug efficacy. For example, excision repair cross-complementation 1 (ERCC1) is involved in the repair of DNA strand cleavage and damage. Its expression affects DNA repairing. The mRNA expression and cisplatin efficacy of ERCC1 are reversely correlated.^{6,7} The negative correlation was also observed between the mRNA expression level and FU efficacy of thymidylate synthetase (TYMS),^{8,9} the mRNA expression and gemcitabine efficacy of ribonucleotide reductase M1 (RRM1),^{10,11} and the mRNA expression and taxol efficacy of β -tubulin isotype III (TUBB3).^{12,13} Therefore, the mRNA expression of these four genes in tumor was examined, and drugs and radiation dose for treatment were chosen according to their expression levels.

To improve the clinical efficacy, this study explored the selection of drug based on oncogene expression in nonsurgical esophageal squamous cell carcinoma (ESCC) patients, under the same circumstance of radiotherapy target volume dose and irradiation technology.

Patients and methods

Study design

This is a retrospective study that included 36 ESCC patients treated at the Center for Oncology of Shandong Provincial Hospital, affiliated to the Shandong University, People's Republic of China, from December 1, 2010, to November 1, 2013. The inclusion criteria for this analysis were as follows: those having pathologically defined esophageal cancer based on computed tomography (CT) scanning and

stages II–IV based on the American Joint Committee on Cancer classification¹⁴ (only supraclavicular lymph node metastasis for stage IV); no distant metastasis, Eastern Cooperative Oncology Group performance status¹⁵ of 0–2; no penetration; adequate bone marrow, renal, and hepatic function; and disease measurable or evaluable by Response Evaluation Criteria in Solid Tumors (RECIST) criteria.¹⁶ This study was approved by the ethics committee of the Shandong Provincial Hospital, Shandong University. Written informed consent was obtained from all patients. Patients having previous malignancy, allergic to cisplatin or docetaxel, or pregnant or lactating were excluded from this study.

Specimen collection and gene expression analysis

Three to four pieces of tumor tissues were collected in the first esophagus endoscopic examination. The study required a collection of formalin-fixed and paraffin-embedded tumor specimens before the therapy. All specimens used in this study were 5 μ m-thick sections of paraffin-embedded tissue. The mRNA levels of ERCC1, TYMS, RRM1, and TUBB3 in the tumor sample were measured by a branched DNA liquid chip. The mRNA measurement was performed using Surexam (Guangzhou, People's Republic of China), which included the following steps: 1) an appropriate amount of formalin-fixed and paraffin-embedded sample was added into a lysate buffer and incubated at 56°C for 2 hours. 2) For prehybridization, the lysate was added into a plate containing probe microspheres, extending the probe and buffer and incubating overnight at 55°C in a shaker. 3) The supernatant was removed, and the plate was put on a magnetic rack for 1 minute; the supernatant was removed after the magnetic beads gathered at the bottom. 4) Washing buffer was added and the solution was vortexed for 1 minute. The plate was put on the magnetic rack again for 1 minute, and the supernatant was removed. The washing steps were repeated for three times. 5) For hybridization, an amplification probe and a labeling probe were added into the plate at 50°C for 1 hour with shaking. 6) The plate was then put on the magnetic rack for 1 minute, and the supernatant was removed. The beads were washed twice using the washing buffer. 7) For signal amplification, streptavidin-conjugated phycoerythrin was added into the plate at 50°C for 30 minutes. 8) The plate was then put on the magnetic rack for 1 minute, and the supernatant was removed. The beads were washed twice with the washing buffer. 9) Washing buffer was added and incubated for 5 minutes, and data were acquired using

Luminex. 10) The data were analyzed, and the test results were obtained. The gene expression was divided into three classes: high ($\geq 75\%$), medium ($< 75\%$ and $\geq 25\%$), and low ($< 25\%$ and $\geq 0\%$), compared with that of thousands of cases in the Chinese Esophageal Population Database.

Procedures

Treatment plan

Pathologically confirmed ESCC patients were examined with esophageal barium meal; enhanced CT examination for neck, chest, and upper abdomen; whole body bone scan; blood cell count; and liver and kidney function tests. The mRNA expression of ERCC1, TYMS, RRM1, and TUBB3 in the tumor tissue was determined within five working days. Patients were grouped and treated with chemoradiation therapy and cisplatin, 5-FU, gemcitabine, or docetaxel according to the expression levels of ERCC1, TYMS, RRM1, and TUBB3. Cisplatin, 5-FU, gemcitabine, and docetaxel were used for patients with a low expression of ERCC1, TYMS, RRM1, and TUBB3, respectively. Cetuximab is chosen for patients in whom all four genes were highly expressed. In principle, a combinational therapy with two drugs was used for chemotherapy, except for patients with low expression in only one tested gene when a single drug was used. For example, cisplatin was used as a synthetic radiation drug for patients with low ERCC1 expression but high TYMS, RRM1, and TUBB3 expression. The drug dosages used were as follows: cisplatin 15 mg/m² from day 1 to day 5; 5-FU 500 mg/m² from day 1 to day 5; gemcitabine 1,000 mg/m² on day 1 and day 8; docetaxel 60 mg/m² on day 1 and every 28 days; and cetuximab 400 mg/m² on day 1, followed by weekly doses of 250 mg/m² for 7 weeks in total.

The intensity-modulated radiation therapy was used in this study for the treatment; gross tumor volume included esophageal tumor and positive lymph nodes; clinical target volume included the esophagus that surrounds 3–4 cm of tumor tissues and the corresponding normal esophageal lymphatic drainage area, and the remaining 5 mm of normal tissue, thoracic, and cervical esophagus carcinoma including bilateral supraclavicular region and the portion of the lower neck region. Planning target volume was based on clinical target volume with a margin of 5 mm. A total radiation dose of 60–66 Gy was applied with 2 Gy fractions delivered 5 days/wk; 95% of the reference dose covered $>90\%$ planning target volume based on the isodose curve. The maximum allowable dose for the spinal cord was restricted to ≤ 50 Gy, and the volume of both lungs that receive >20 Gy (the V20) would not exceed 30% of the total.

Response evaluation

Disease response was evaluated according to the RECIST V1.1.¹⁶ Efficacy was evaluated using chest CT and esophageal endoscopy combined with esophageal barium meal 1 month after chemoradiation therapy. Evaluation criteria were divided into complete remission (lesions disappear, chest CT scan shows esophageal wall thickness < 10 mm, enlarged lymph nodes disappear, smooth esophageal mucosa seen under endoscopic observation, and esophageal barium meal shows disappearance of filling defects), partial remission (PR, at least a 30% decrease in the sum of the greatest dimensions of target lesions, relative to the baseline sum of greatest dimensions), stable disease, and progressive disease. Acute adverse reaction is evaluated according to the American radiotherapy tumor tissue acute radiation injury classification criteria. The blood cell count was examined every week. Liver and kidney functions were tested before chemotherapy. Chest CT and esophageal barium meal examinations were performed for each 20 Gy radiation therapy.

Follow-up

Patients were followed up every 3 months for the first year after treatment, every 6 months between 1 year and 3 years, and once a year after that. Routine physical examination; blood cell count; liver and kidney function tests; esophageal barium meal; and neck, chest, and upper abdominal CT were performed during each visit with additional esophagus endoscopic examination for esophageal barium meal abnormal.

Statistical analysis

Statistical analyses were performed using the SPSS statistical software (Version 17.0; SPSS Inc., Chicago, IL, USA). The Kaplan–Meier method was used for survival analysis, and differences in survival were estimated using the log-rank test. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics and treatment

A total of 39 patients were registered onto the trial from December 1, 2010, to November 1, 2013. Of these, 36 patients were enrolled into the study and three were excluded due to inadequate tissue for analysis. Two patients who had high expression of ERCC1, TYMS, RRM1, and TUBB3 were treated with cetuximab. The regimen used for chemoradiotherapy was cisplatin/5-FU (PF) for 15 cases, gemcitabine/cisplatin for three cases, cetuximab for two cases, cisplatin for eight cases, docetaxel for two cases, and docetaxel/cisplatin for six cases (Figure 1). Characteristics

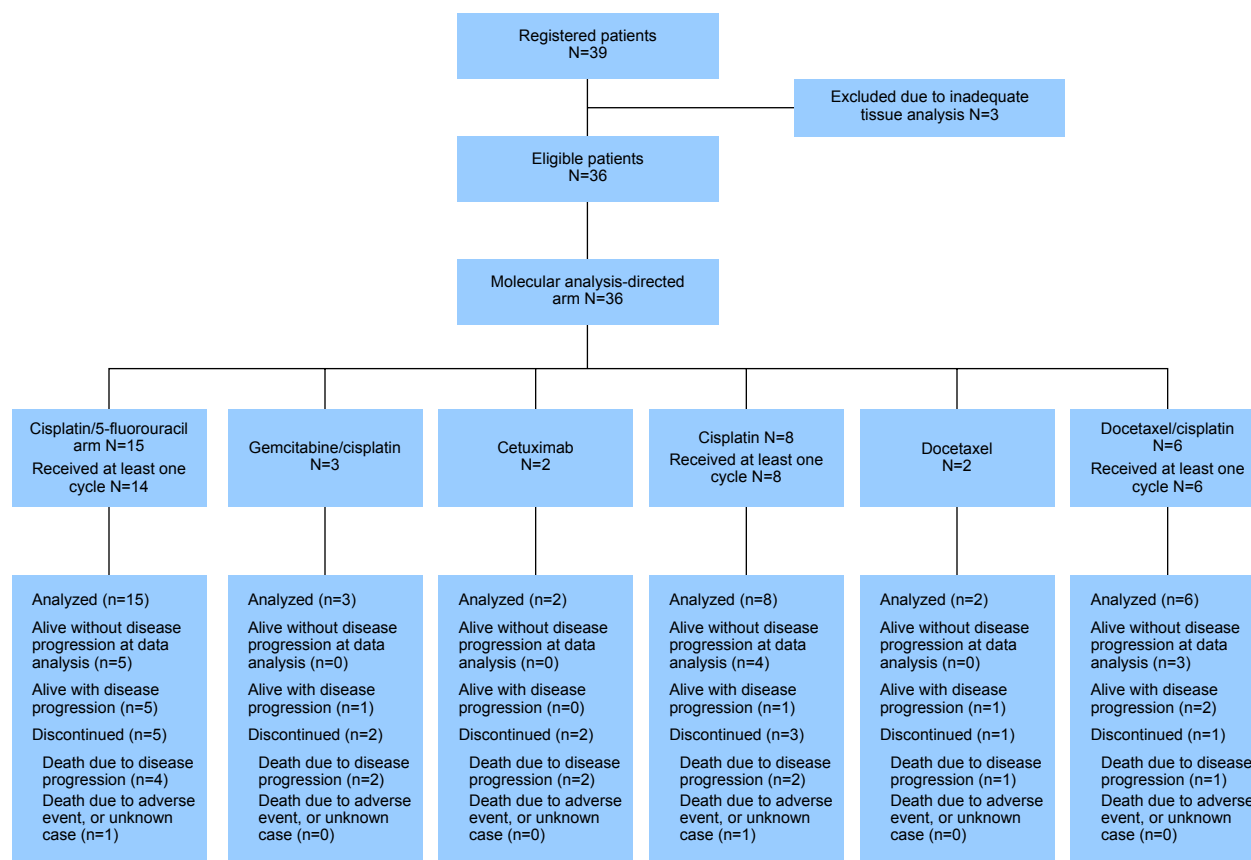


Figure 1 Flowchart of patient characteristics and treatment.

Note: Progression meets the Progressive Disease criteria of RECIST1.1.

of the 36 eligible patients are summarized in Table 1. Four patients were >70 years old, with the oldest one being 74 years. The number of female patients was eight. Pathological types were squamous cell carcinoma for all the patients (Table 1). The dose used for radiation therapy was as follows: one case with 42 Gy, two cases with 48 Gy, 22 cases with 60 Gy, and eleven cases with 66 Gy. Patients who had completed one course of chemotherapy were as follows: two patients in the DP therapy group; one patient in the PF therapy group; and one patient in the GP therapy group.

The mRNA levels of ERCC1, TYMS, RRM1, and TUBB3 were determined using a liquid chip and were divided into low, medium, and high levels (Figure 2). Twelve patients had a low ERCC1 expression and three patients had a high ERCC1 expression level. The number of patients with high expression of TYMS, RRM1, and TUBB3 was 12, 11, and 16, respectively.

Disease response

The therapeutic efficacy and response rate for each treatment are summarized in Table 2. Among the 36 patients, 25 (69.4%), five (13.9%), three (8.3%), and three (8.3%)

patients achieved CR, PR, stable disease, and progressive disease, respectively, after treatment.

Surveillance

The patient follow-up time was 1.18–41.2 months with a median of 30.06 months. The last follow-up was recorded on October 1, 2015. At the end of this study, 22 patients survived, 14 patients died, 22 patients got relief, 12 patients achieved complete remission, and ten patients with disease progression remained alive. The median follow-up time was 26.48 months.

Progression-free survival and overall survival (OS) rates are shown in Figure 3. The OS rates for the first, second, and third year were 83.3%, 68.1%, and 58.4%, respectively. The progression-free survival rates for the first, second, and third year were 79.8%, 58.9%, and 54.4%, respectively. The relationship between the patient survival rate and mRNA level of ERCC1, TYMS, RRM1, and TUBB3 is shown in Figure 4. A correlation exists between the ERCC1 gene expression and patient's OS, with a significant difference between the ERCC1 high and low groups ($\chi^2=5.048$; $P=0.024$). No significant difference was found in OS rates

Table 1 Patient characteristics (N=36)

Characteristics	Variable	No (%)
Age, years	41–50	7 (19.4)
	51–60	11 (30.6)
	61–70	14 (44.4)
	≥70	4 (11.1)
Sex	Male	28 (77.8)
	Female	8 (22.2)
Location	Upper	6 (16.7)
	Middle	19 (52.8)
	Lower	11 (30.6)
Histological grade	G1	7 (19.4)
	G2	20 (55.6)
	G3	9 (25.0)
Tumor length, cm	≤5.0	21 (58.3)
	5.1–7.0	11 (30.6)
	>7.0	4 (11.1)
CT	T1	0 (0)
	T2	14 (38.9)
	T3	13 (36.1)
	T4	9 (25.0)
CN	N0	11 (30.6)
	N1	14 (38.9)
	N2	11 (30.6)
	N3	0 (0)
CTNM stage ^a	IIa	3 (8.3)
	IIb	9 (25.0)
	IIIa	10 (27.8)
	IIIb	8 (22.2)
	IIIc	3 (8.3)
	IV	3 (8.3)

Note: ^aAmerican Joint Committee on Cancer Staging Manual 2009 classification 7th edition.

Abbreviations: CN, lymph node clinical stage; CT, tumor clinical stage; CTNM, TNM clinical stage.

among groups with different TYMS, RRM1, and TUBB3 expression.

Safety

Among the 36 patients, three did not complete treatment, one stopped treatment at the 48 Gy radiotherapy dose due to acute radiation pneumonitis, one stopped treatment at the same dose due to grade IV thrombocytopenia, and one stopped treatment at the same dose due to esophageal fistula mediastinal radiotherapy. Nineteen cases had hematological toxicity severe than grade III. Four patients had acute radiation pneumonitis with one patient having grade III radiation pneumonitis; ten patients had radiation esophagitis with

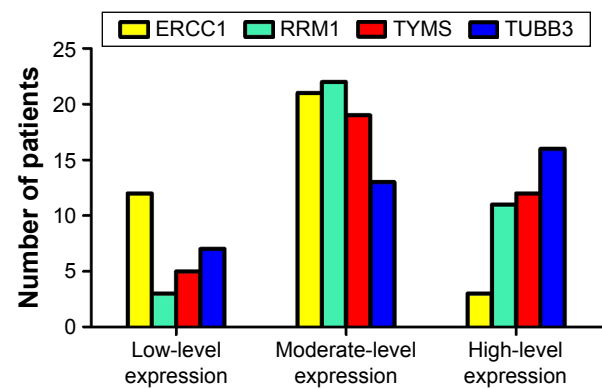


Figure 2 The number of patients with each genotype based on expression levels. **Abbreviations:** ERCC1, excision repair cross-complementation 1; RRM1, ribonucleotide reductase M1; TYMS, thymidylate synthetase; TUBB3, β -tubulin isotype III.

severity greater than grade II; eight cases of the patients with grade III, including two cases in the GP group: one case had mediastinal esophageal fistula and one had fistula.

Discussion

Chemoradiation therapy was given to 36 patients with nonsurgical ESCC with an overall response rate (CR + PR) of 83.3%. The 1-year, 2-year, and 3-year survival rates were 83.3%, 68.1%, and 58.4%, respectively. A high correlation between the mRNA level of ERCC1 in tumor tissue and the patient's survival was observed ($\chi^2=5.048$; $P=0.024$).

The short-term efficacy of esophageal chemoradiotherapy was 89.5%–98% in previous studies.^{17–19} 5-FU + DDP was used as a chemotherapy drug in chemoradiation therapy. Previous studies showed that regimens including taxol had a better effect compared with 5-FU + DDP therapy.^{20,21} Different drugs combined with radiotherapy may have their own advantages. A meta-analysis¹⁹ also supported that chemoradiation therapy containing taxol had a better short-term effect than that with 5-FU + DDP. The results from the present study were similar to those from others. The overall response rate (CR + PR) was 100% in eight cases treated with therapy containing docetaxel (two cases used docetaxel alone and six cases used DP). It should be noted that in this study, eight patients were treated with cisplatin alone and two patients were treated with docetaxel alone, accounting for 27.8% of total subjects in the group (10/36).

The results of the present study showed that 1-year, 2-year, and 3-year survival rates were 83.3%, 68.1%, and 58.4%, respectively, for such patients. The 2-year and 3-year survival rates were 36% and 30%, respectively, for the chemoradiation therapy group in the RTOG85-01 study.

Table 2 Impact of different treatment regimens on disease response

Outcome	All (N=36)		R + PF (N=15)		R + C225 (N=2)		R + GP (N=3)		R + P (N=8)		R + D (N=2)		R + DP (N=6)	
	No	%	No	%	No	%	No	%	No	%	No	%	No	%
CR	25	66.6	12	80.0	1	50.0	1	33.3	4	50.0	1	50.0	6	100.0
PR	5	11.1	1	6.7				33.3	2	25.0	1	50.0		
SD	3	13.9			1	50.0	1	33.3	1	12.5				
PD	3	8.3	2	13.3						1	12.5			

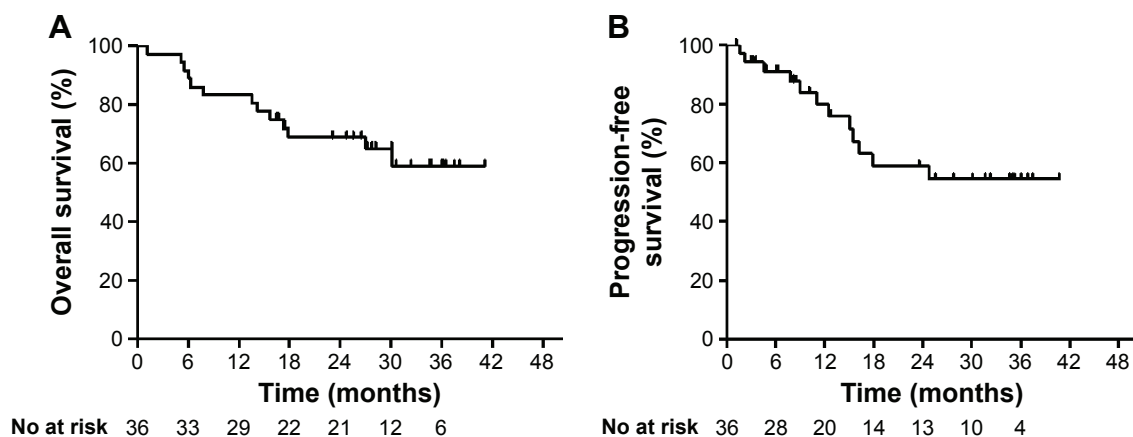
Abbreviations: C225, cetuximab; CR, complete remission; DP, docetaxel/cisplatin; GP, gemcitabine/cisplatin; PF, cisplatin/5-fluorouracil; D, docetaxel; R, radiotherapy; P, cisplatin; PD, progressive disease; PR, partial remission; SD, stable disease.

In the same study, 2-year and 3-year survival rates were 40% and 33% in the low-radiation dose group (50.4 Gy), and 31% and 25% in the high-radiation dose group (64.8 Gy), respectively. Similarly, although the efficacy of concurrent chemoradiotherapy is significantly improved compared with that of radiotherapy alone for esophageal cancer treatment in the People's Republic of China, the effect is still not high. For ESCC patients, 2-year and 4-year survival rates were 35%–58% and 20%–51%, respectively, under chemoradiation therapy containing 5-FU + DDP.²² Although chemoradiation therapy containing taxol improves the short-term response, 1-year and 3-year survival rates do not increase. Li et al¹⁸ reported that the 1-year and 3-year OS rates were 81% and 36.5%, respectively, for nonsurgical ESCC patients treated with chemoradiation therapy, including docetaxel and cisplatin, and a radiation dose of 60–64 Gy, whereas the 1-year and 3-year OS rates were 84.4% and 45.6%, respectively, for advanced esophageal cancer treated with 5-FU, cisplatin, and a radiation dose of 60 Gy. Zhang et al²³ treated 90 cases of locally advanced esophageal cancer with docetaxel plus cisplatin (PF regimen) in combination with radiotherapy group or radiotherapy concurrent with PF regimen treatment, and the 3-year survival rates were 23.9% and 12.1%, respectively. The reason is that the

patients were enrolled in the later clinical stage, and ~25% of patients cannot tolerate chemotherapy with hematologic toxicity leading to termination of chemotherapy. Ji et al²⁴ reported 160 cases of locally advanced esophageal cancer: patients were randomly divided into intensity-modulated radiotherapy combined with docetaxel plus cisplatin group and intensity-modulated radiotherapy alone group, and the 5-year survival rates were 29.3% and 15.3%, respectively. These data indicate that long-term survival of patients with inoperable esophageal cancer after chemoradiotherapy needs to be further improved.

Although the number of cases included in this study was limited, the 3-year survival rate was >50% after treatment, especially with three patients in stage IV: one patient had lower esophageal retroperitoneal lymph node metastasis and two patients had supraclavicular lymph node metastasis (one is in the bottom and another one is in the middle). The survival time of these three patients was 5.7 months, 6.5 months, and 41.2 months, respectively. Although a negative result was observed for choosing lung cancer chemotherapy regimens based on gene expression, the interpretation of this study was largely due to a rational drug selection.²⁵

In this study, the expression of ERCC1 was highly correlated with patient survival in esophageal carcinoma. Patients

**Figure 3** (A) Overall survival and (B) progression-free survival for all cases.

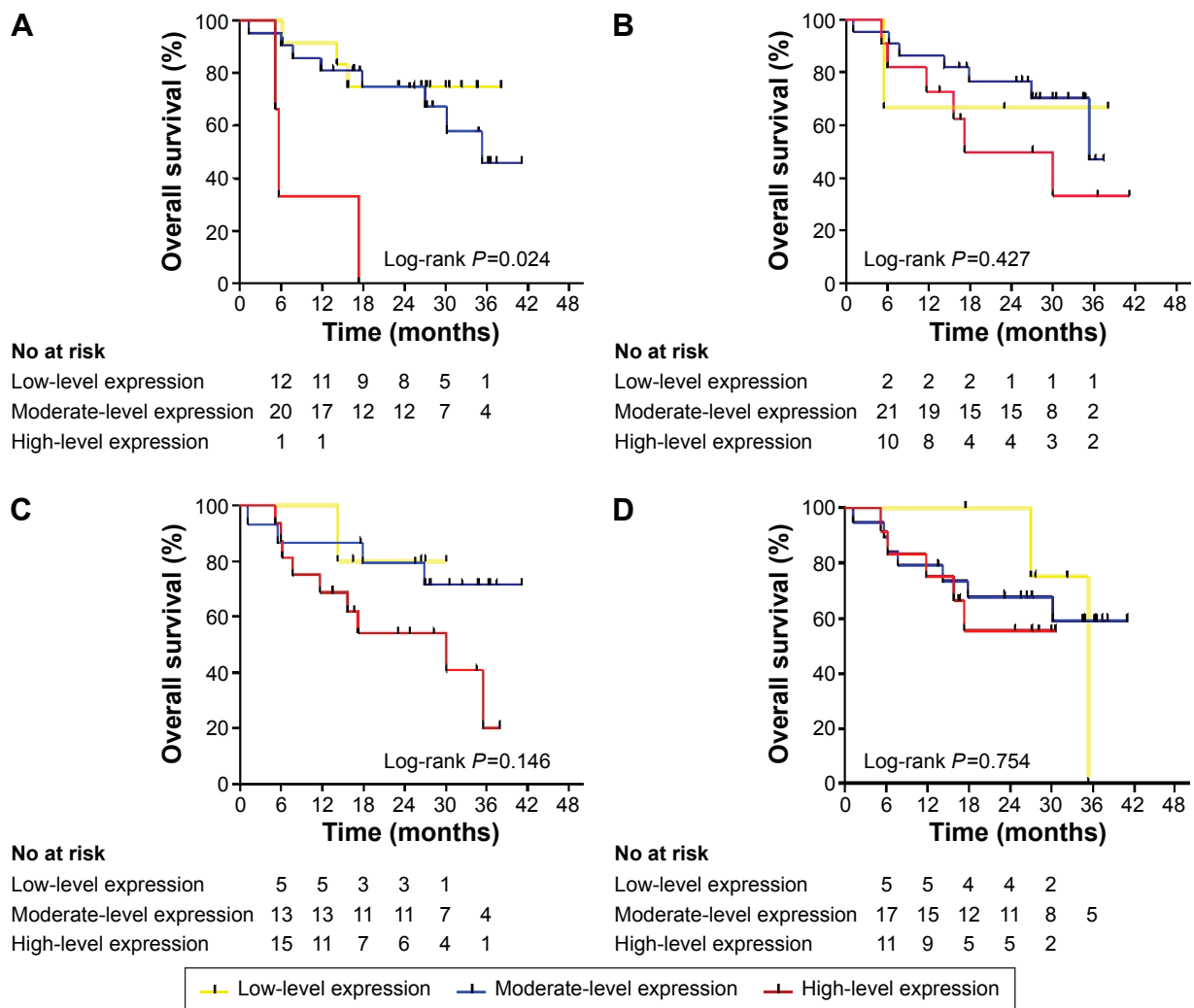


Figure 4 Comparison of overall survival among the expression levels of genotype (A) ERCC1, (B) RRM1, (C) TYMS, and (D) TUBB3.

Abbreviations: ERCC1, excision repair cross-complementation I; RRM1, ribonucleotide reductase M1; TYMS, thymidylate synthetase; TUBB3, β -tubulin isotype III.

with a high ERCC1 expression had a poor prognosis than those with low expression. The use of ERCC1 as a diagnostic marker for esophageal carcinoma is controversial. High expression of ERCC1 mRNA in esophageal carcinoma, before adjuvant chemoradiotherapy, was reversely correlated with remission.^{26,27} However, the OS did not change despite better remission observed in ERCC1-negative tumor.²⁸ In another study including 175 cases of esophageal carcinoma, ERCC1-negative patients benefited from cisplatin before surgery, but high ERCC1 expression was correlated with better long-term prognosis.²⁹ This study showed a poor prognosis in high ERCC1 expression patients, two cases out of the three patients were cT4N1M0 IIIc stage, and another one case was cT3N1M0 IIIa stage. All the patients were in the late clinical stage. It indicated that late clinical stage and poor prognosis were associated with late stage of TNM. This phenomenon prompted that ESCC with high ERCC1 expression may be the reason for majority of patients with

advanced stage for the initial diagnosis. The correlation between the survival and expression of TYMS, RRM1, and TUBB3 was not observed.

This study had some limitations. First, the genome and tumor heterogeneity will affect an individual's response to drugs. It is still immature to guide tumor chemotherapy based on genetic information. The conclusion has inevitable bias due to small sample size. Second, the present study was conducted in a single institute, not a randomized controlled study. Third, the follow-up time was only 30.06 months, and a longer follow-up is necessary for long-term survival results.

Conclusion

The results showed that genetic information-guided esophageal chemoradiation therapy can improve the survival rate, but further studies with a larger number of cases are necessary.

Disclosure

The authors report no conflicts of interest in this work.

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