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A Molecular Biomarker Prediction Model for Preoperative Radiosensitivity in Rectal Cancer: An Analysis of 33 Patients' Information

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1. Abstract

1.1. Objective: Investigate the correlation between radio-sensitivity related biomarkers and preoperative Radiotherapy (pRT) in rectal cancer patients, and try to establish a logistic regression model, which can predict the response of the pRT through the expression levels of the molecular markers.

1.2. Methods: A retrospective study was carried out. Patients with rectal cancer receiving pRT were screened-- 33 in total. Patients' information's including the serum level of CEA, the Immune-Histochemical(IHC) expression levels of VEGF、EGFR、TS、−Ki-67 and image data (MRI) before and after the radiotherapy were collected. According to the image data before and after the radiation, the treatment effects including response (CR + PR) and non-response (PD+SD) were evaluated. The relationships between the molecular markers and the effect of pRT were analyzed by logistic regression analysis by using SPSS v17.0 and a logistic regression prediction model was established.

1.3. Results: As a result of the logistic regression analysis, CEA、VEGF、Ki-67 were recognized as the relevant factors for the radio-sensitivity predicting in patients with rectal cancer that received pRT. Serum CEA level and the expression of VEGF might be associated with radio-resistance and the expression of Ki-67 might be associated with better response.

1.4. Conclusion: CEA, VEGF and Ki-67 were the predictors of radio-sensitivity in rectal cancer patients; high levels of serum CEA and IHC expression of VEGF related to poor tumor regression and Ki-67 has an opposite effect. Levels of EGFR and TS have little correlation with tumor response. We conducted a prediction equation based on the data before.

2. Introduction

Rectal cancer is one of the most common cancers that threatens human health, the incidence of rectal cancer is rising in recent years [1-2]. Surgery is the most common curative therapy and the Total Mesorectal Excision(TME) can help improving the local control of rectal cancer. However, the recurrence rate of locally advanced lesions is still high. The pRT is usually applied to stage II/III rectal cancer (T3-4N0 or N+) [3] and can decrease the recurrence rate [2]. It can lead to tumor regression and its down- staging, then improves the rate of definitive resection and local control, and improves the rate of anal preservation from 40% to about 60%, so that it provides the patients a better living quality [4-6]. More and more researches in last decades proved that pRT can improve local control and the rate of anal preservation. However, the overall survival rate was not significantly improved [7-9]. Several clinical researches reported that pRT has priority to postoperative radiotherapy in improving local control and the rate of anal preservation [10-12]. Based on the current evidences, the treatment mode of locally advanced rectal cancer is pRT with sequential surgery and adjuvant therapy, which was suggested by NCCN guidelines.

The pRT is beneficial in most situations. There are still some patients which are radio-resistant to the treatment. For these patient's radiotherapy was not beneficial but harmful because of the severe adverse effects. And the preoperative treatment even make the patients lose the opportunity for definitive surgery because of tumor progression during the long course of radiation. If we can find a model which can predict the response rate of pRT, then we can distinguish patients that may benefit from pRT or not, and treat these patients differently.

Several retrospective researches indicated that serum level of CEA and the expression of biomarkers like VEGF, EGFR, TS and Ki-67 may be relative to the response rate in preoperative radiation of locally advanced rectal cancer [13-19]. Also these markers may have particular predictive values in some cases. However, the predictive value of a single marker is only limited for the research of tumor genesis, which is a multi-mechanism process. So, combined analysis of several biomarkers simultaneously, it may provide a better prediction. In our research, we tried to predict the response of pRT in rectal cancer patients via serum CEA, the immunohistochemical expressions of VEGF, EGFR, TS and Ki-67.

3. Methods and Materials

3.1. Patients and Methods

From June 2009 to June 2014,'clinical information of 33 rectal cancer patients in the First affiliated hospital of Kunming medical university were collected for a retrospective analysis. All patients had undergone pRT. Pathological specimens from colonoscopy before the radiation were used to detect the expression level of VEGF, EGFR, TS and Ki-67 of each patient via immunohistochemical method. Serum CEA levels before the radiotherapy were obtained from the hospital information system. The MRI images before the radiotherapy and 8 weeks after radiotherapy of each patient were obtained from picture archiving and communication system(PACS). Of all selected patients, the age ranged from 29 to 81 years, the mean age was 59.3 years and the median age was 61 years. There were 22 males and 11 females. All patients were diagnosed with rectal cancer through pathology。

3.2. Detection of the Molecular Bio-Markers

3.2.1. The level of serum CEA was detected by chemiluminescent immunoassay and the expressions of VEGF, EGFR, TS and Ki-67 were detected by immunohistochemical method.

3.2.2. Each patients' immunohistochemical expression level of VEGF, EGFR, TS and Ki-67 were read out in five random x400 fields of microscope. 100 tumor cells were counted in every field. The positive cells were stained yellow, brown or isabelline, and the negative cells were stained mazarine. The average ratio of positive cells of the five fields was taken as the expression level of each bio-markes of each patients (Figure 1-4).

3.3. The effects of pRT were divided into response-group and non-response-group. The response cases reached a complete response(CR) or partial response(PR) after pRT according to the response evaluation criteria in solid tumors version 1.1(RECIST 1.1) by MRI image. And the non-response cases were those that had a stable disease(SD) or progressed disease(PD) after radiation (table 1).

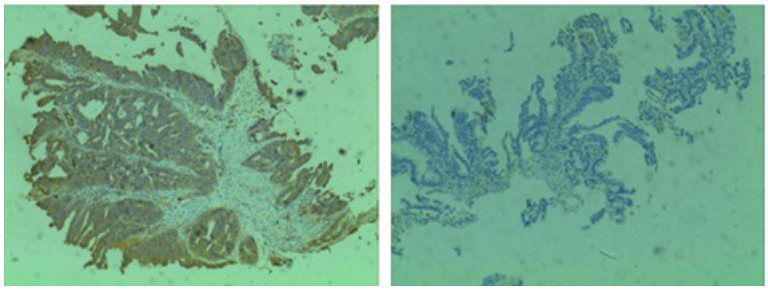

Figure 1: VEGF positive (SP, ×400); VEGF negative (SP, ×400)

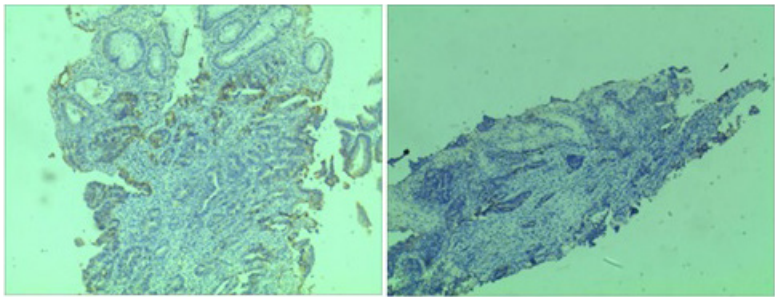

Figure 2: EGFR positive (SP, ×400); EGFR negative (SP, ×400)

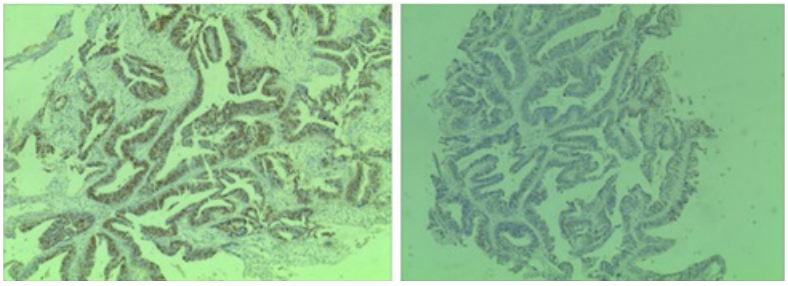

Figure 3: Ki-67 positive (SP, ×400); Ki-67 negative (SP, ×400)

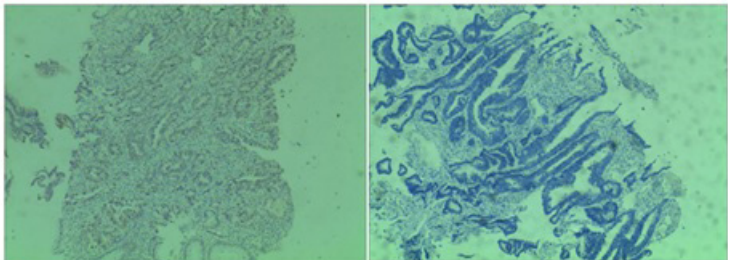

Figure 4: TS positive (SP, ×400); TS negative (SP, ×400)

Table 1: The levels of bio-markers and the response of tumors to preoperative radiation

	Sex	Age	VEGF	EGFR	TS	Ki-67	CEA	Tumor Response
1	M	50	0	0	0	0	1.18	Y
2	F	45	5%	20%	0	0	2.3	N
3	M	75	10%	0	0	20%	2.24	Y
4	M	52	5%	0	0	50%	1.83	N
5	F	61	0	0	0	40%	0.66	Y
6	F	29	20%	0	0	40%	19.3	N
7	M	46	10%	0	0	50%	6.8	Y
8	F	66	10%	0	0	60%	15	N
9	F	58	0	0	0	5%	11.87	N
10	M	65	0%	2%	0	2%	14.06	Y
11	F	58	50%	0%	5%	10%	2.74	N
12	M	59	20%	5%	0	0%	1.38	N
13	M	69	0	0	0	60%	0.9	Y
14	M	64	0	0	2%	40%	19.424	Y
15	M	61	0	0	0	10%	0.93	Y
16	F	53	30%	3%	0	0	2.03	N
17	F	57	0	0	0	0	8.2	N
18	F	36	0	0	0	10%	2.95	N
19	M	41	0	10%	60%	0	2.7	Y
20	M	70	3%	0	0	40%	0.52	Y
21	M	62	0%	0	0	0%	18.48	N
22	M	60	10%	0%	0	0	2.73	N
23	M	71	5%	0	0	20%	3.79	Y
24	M	40	3%	2%	0	20%	0.2	Y
25	M	63	0	0	0	0	1.57	Y
26	F	53	0	0	0	0	2.35	N
27	M	63	0%	40%	0	0	0.63	N
28	M	81	0	0	0	0	1.66	Y
29	M	70	0%	0	0	0%	19.21	N
30	M	69	0	0	0	0	1.3	Y
31	M	75	0	10%	15%	0	2.8	Y
32	M	69	50%	0%	0	0	8.97	N
33	F	67	15%	0	0	60%	3	Y

3.4. Treatment

All patients, who received pRT and concurrent chemotherapy of Xeloda or 5-Fu/Lv, got a local advanced rectal cancer. The radiotherapy technology was three dimensional conformal radiation therapy (3-D CRT) to the primary tumor and lymphatic drainage area. The dose of raidotherapy was 50Gy in 25 fractions in 5 weeks. Before the patients received the radiotherapy or chemotherapy, they were well informed and signed an informed consent.

3.5. Statistic Analysis

The relationship between all the bio-markers above and the effects of pRT were analyzed by univariate or multiple logistic analysis via SPSS17.0. In univariate analysis, the value P<0.1 was taken as statisticly significant. In multiple analysis the P factor used two-tailed probability, and its value P<0.05 was taken as statisticly significant. Then a logistic regression model was established to predict the effect of pRT in rectal cancer patients.

4. Results

4.1 Univariate Logistic Regression Analysis

Based on the expression levels of the bio-markers of 33 patients, univariate logistic regression analysis was done to identify the potential factors that may be associated to the preoperative effect. The results were as follows. The serum level of CEA (OR=0.889, P=0.070) and the IHC expression level of VEGF (OR=0.911, P=0.073) were negatively correlated to the response to radiation, which indicated that rectal cancers with high levels of CEA or VEGF may have a poor response to radiation. The levels of EGFR (P=0.305>0.1) and TS (P=0.494>0.1) were not related to tumor response. The level of Ki-67 was positively related to tumor regression (OR=1.038, P=0.066), which might mean that cancer with a high level of Ki-67 has a better response to radiation (table 2).

Table 2: Univariate logistic regression analysis

	P-value	OR	95%C.I. of OR
CEA	0.07	0.889	0.782-1.010
VEGF	0.073	0.911	0.823-1.009
EGFR	0.305	0.936	0.826-1.062
TS	0.494	1.116	0.815-1.529
Ki-67	0.066	1.038	0.998-1.080

4.2. Multiple Logistic Regression Analysis

According to the results of the multiple logistic regression analysis, high levels of serum CEA (OR=0.759, P=0.031) and VEGF (OR=0.788, P=0.045) were related to worse tumor regression after preoperative radiation, and levels of EGFR (P=0.334>0.05) and TS (P=0.262>0.05) were not related to tumor response. On the opposite, high levels of Ki-67 (OR=1.083, P=0.033) might have a better tumor response (table 3).

Table 3: Multiple logistic regression analysis

	Regression coefficient	Standard error	P-value	OR	95%C.I. of OR
CEA	-0.276	0.128	0.031	0. 759	0.591-0.975
VEGF	-0.238	0.124	0.045	0.788	0.618-1.005
EGFR	-0.135	0.14	0.334	0.873	0.664-1.149
TS	1.377	1.229	0.262	3.961	0.357-44.011
Ki-67	0.08	0.038	0.033	1.083	1.006-1.166

4.3 Prediction Model

Based on the logistic regression analysis, an equation was established to try to predict the radiosensitivity of preoperative in rectal cancer patients as below.

Log P=1.700-0.276×CEA-0.238×VEGF-0.135×EGFR+1.377×TS +0.080×(Ki67)

Sig: [Unit of serum CEA is ug/L,the levels of VEGF,EGFR,TS and Ki-67 were the ratio of positive cells in IHC (%)]

5. Discussion

More and more evidences support neoadjuvant radiotherapy/pRT instead of postoperative/adjuvant radiotherapy because of the superiority in local control and PFS. Also there are so many advantages, the cancer radioresistance bothered radiotherapy physicians. As the researchers reported, about 35%-50% locally advanced rectal cancers were radiosensitive, and nearly 50% were not [20-21]. For these patients, radiotherapy may be harmful because of bad tumor regression and radiation-related injury, lots of patients even lost the chances to have the definitive surgery because of tumor progression or metastasis during the radiotherapy. So finding a way to predict the responses to radiotherapy may helpful.

In our research, we retrospectively analyzed the pathological sections and serum CEA of 33 rectal cancer patients who underwent pRT. Based on the relationship between CEA, VEGF, EGFR, TS, Ki-67 and tumor responses, we conducted an equation to try to predict the radiosensitivity. According to the equation, the P value is between 0-1. If the value gets more close to 1, then the cancer may be more radiosensitive, and if it gets close to 0, it means the cancer is almost radioresistent. The methods were firstly reported by us, and they may be useful in clinical application.

However, there may be several limitations in our research. Firstly, the statistical sample of our research is relatively small, so that there may be some biases which may affect the accuracy of the equation. Secondly, in our research, some macroscopical factors were not well considered, like the pathological pattern, the pathological grading or the tumor size. These factors may have a far-reaching influence on the effect of radiotherapy. Thirdly and the lastly, because of the limited budget, we used IHC to detect the levels of bio-markers, which was behindhand when compared

to PCR etc. Even though our attempt is encouraging because the mechanism of tumor genesis is a multiple-factors attended process. We will in the future consider more factors that may affect the radio-sensitivity and provide a more compellent equation for the predicting.

6. Conclusion

Our research indicated that CEA, VEGF and Ki-67 were the predictors of radio-sensitivity in rectal cancer patients; high levels of serum CEA and IHC expression of VEGF was related to poor tumor regression and Ki-67 has an opposite correlation. Levels of EGFR and TS have little correlation with tumor response. Based on the data before, we suggested a prediction equation as below:

Log P=1.700-0.276×CEA-0.238×VEGF-0.135×EGFR+1.377×TS +0.080×(Ki67).

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