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***Retrospective Study***

**Effects of omeprazole on improving concurrent chemoradiotherapy efficacy in rectal cancer**

Zhang JL *et al*. Omeprazole improves chemoradiotherapy efficacy

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**Abstract**

***AIM***

To explore the effects of omeprazole on chemoradiotherapy efficacy and tumor recurrence in rectal cancer.

***METHODS***

The medical data of 125 rectal cancer patients who received the same neoadjuvant chemoradiotherapy (CRT) followed by surgery were retrospectively collected. Patients who received omeprazole (OME) orally at a dose of 20 mg at least once daily for six days and/or intravenously at 40 mg a day were recognized as eligible OME users (EOU). Otherwise, patients were regarded as non-eligible OME users (non-EOU). Moreover, a preferred OME dose cut-off of 200 mg on tumor recurrence was obtained by receiver operating characteristic (ROC) curves. Patients were divided into the following two groups: the effective OME group (EOG, OME ≥ 200 mg) and the non-effective OME group (non-EOG, OME < 200 mg).

***RESULTS***

The good response rate of CRT efficacy (50.8%) in EOU was significantly increased compared with non-EOU (30.6%) (*p =* 0.02). The recurrence rate in the EOG was 10.3%, which was significantly reduced compared with 31.3% in non-EOG (*p =* 0.025). The good response rate of CRT efficacy in EOG was 55.2%, which was obviously increased compared with 36.5% in non-EOG, with a marginally significant difference (*p =* 0.072). Multivariate Cox analysis demonstrated that OME (non-EOG and EOG) was an independent and signiﬁcant impact factor for DFS (*p =* 0.048, HR = 0.30, 95%CI: 0.09-0.99).

***CONCLUSION***

when applied as an adjuvant drug in cancer treatment for relieving common side effects of chemotherapy, omeprazole has a synergetic effect on improving CRT efficacy and decreasing rectal cancer recurrence.

**Key words:** Omeprazole; Chemoradiotherapy efficacy; Recurrence; Rectal cancer

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**Core tip:** In *in vitro* and *in vivo* studies, proton pump inhibitors (PPIs) induce apoptosis of gastric cancer cells, B-cell tumors and hepatoblastoma cells and promote autophagy in melanoma cells and pancreatic cancer cells. PPIs also sensitize chemo-resistant tumors to cytotoxic drugs and improve the efficacy of T-cell-based cancer immunotherapy. However, whether PPIs affect chemoradiotherapy (CRT) efficacy, decrease tumor recurrence and improve survival in rectal cancer patients remains unclear. In the present study, when used as adjuvant drug in cancer treatment, omeprazole has a synergetic effect on improving CRT efficacy and decreasing recurrences in rectal cancer.

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**Introduction**

Rectal cancer is one of the worldwide leading causes of cancer related death[1]. Preoperative chemoradiotherapy (CRT) followed by radical surgery is a preferred treatment for patients with advanced rectal cancer given reduced local recurrence and high sphincter preservation rate[2-4]. However, disease relapse is still a critical factor that affects patient survival[2]. The exploration of factors that affect CRT efficacy and tumor recurrence are critical to improve cancer management.

Abnormal pH gradients in the tumor microenvironment are involved in tumorigenesis, tumor progression and drug resistance[5-11]. Vacuolar type H+-ATPases (V-ATPases) are proton pumps expressed on the membrane of endolysosomal organelles and plasma membranes[5], which could modulate the tumor acidic microenvironment[12,13]. V-ATPases are overexpressed in chemo-resistant cancer cells and are induced by cytotoxic drugs[14,15], playing a key role in cancer cells with a multidrug resistance phenotype[16]. Proton pump inhibitors (PPIs), such as omeprazole (OME) and esomeprazole, are used to relieve common side effects of chemotherapy, such as nausea and emesis. In addition to targeting the gastric acid pump, PPIs inhibit the activity of V-ATPases[17-20]. Moreover, PPIs induce apoptosis in gastric cancer cells[21], B-cell tumors[22] and hepatoblastoma cells[23] and promote autophagy in melanoma cells[24] and pancreatic cancer cells[25]. PPIs improve the efficacy of T-cell-based cancer immunotherapy[26-28]. In colorectal cancer, it is reported that PPIs re-sensitize drug-resistant cancer colon adenocarcinomas cell lines to cytotoxic drugs[26]

These study results suggest that the application of PPIs may be helpful in improving cancer treatment. However, whether PPIs could affect CRT efficacy, reduce tumor recurrence and improve survival in rectal cancer remain unclear.

**Materials and methods**

***Patients***

From May 2008 to March 2016, the medical records of consecutive rectal cancer patients who received the same neoadjuvant CRT followed by radical surgery were retrospectively collected. Neoadjuvant CRT included three-dimensional conformal radiotherapy (3D-CRT) using a total dose of 46 Gy concurrent with two cycles of oxaliplatin plus capecitabine. The disease was diagnosed by a combination of medical history, physical examination, biopsy, and staging examination, including abdominal ultrasound scan, abdominal-pelvis computed tomography scan, colonoscopy and endoscopic or trans-rectal ultrasonography. Tumors were staged according to the AJCC (2010 edition). Tumor stages before CRT and after surgery were classified as cTNM and ypTNM, respectively. Patients lacking detailed medical records or those with a second tumor or distant metastasis were excluded; thus, 125 patients met the criteria. The patients were aged from 15 to 78 years, with a mean age of 55.8 ± 12.01 years. The mean body weight and mean height of the patients was 60.1 ± 9.3 kg and 164.1 ± 6.85 cm, respectively. Among the 125 patients, pre-treatment serum carcinoembryonic antigen (CEA) and CA19-9 data were available for 120 patients. The study was approved by the Medical Ethics Committee of Sun Yat-Sen University Cancer Center. Written informed consent was obtained from all patients.

***Neoadjuvant concurrent CRT***

Radiation treatment planning was designed according to three-dimensional conformal radiation therapy (3D-CRT), with one posterior ﬁeld and two lateral ﬁelds. Patients were treated using a range of 6 to 15 MV photons. Radiation was delivered in a total dose of 46 Gy (23 fractions with 2 Gy per fraction in 5 wk). Gross tumor volumes (GTVs) included rectal tumors and enlarged lymph nodes. Clinical target volumes (CTVs) included lymphatic drainage areas around the rectum and sacrum. Planning target volume (PTV) included areas with a 0.8 to 1.0 cm radial margin around the CTV. Patients were treated in the prone position, and a belly board was used to exclude the small bowel out of the radiation ﬁeld. Oxaliplatin (130 mg/m2) was delivered intravenously over 2 h on the first day of radiation treatment and on day 21. Capecitabine was administered orally twice daily at 1000 mg/m2 on days 1 to 14 and days 21 to 34.

***Dosage of omeprazole***

Omeprazole usage was recorded in detail. Omeprazole was administered orally at 20 mg twice a day (Omeprazole Magnesium Entericcoated Tablets, AstraZeneca AB), 40 mg (Omeprazole Sodium for Injection, AstraZeneca AB) or 60 mg (Omeprazole Sodium for Injection, Changzhou Siyao Pharmaceuticals Co., Ltd.) intravenously one hour before the start of chemotherapy and was continuously administered in the following days if the patients complained of digestive discomfort. The reduction in gastric peak acid secretion after continuous oral administration of 20 mg OME once daily for six days was comparable with the effect of a single intravenous dose of 40 mg OME[29]. Thus, patients who received 20 mg OME orally at least once a day for six days and/or intravenous infusion of 40 mg OME daily were recognized as eligible OME users (EOU); otherwise, the patients were regarded as non-eligible OME users (non-EOU). Among the 125 patients, 63 patients met the criteria as EOU. Moreover, the bioavailability of oral enteric-coated omeprazole granules is initially low (approximately 35%–40%); however, these levels increased to approximately 65% on repeated dosing[30-33]. Therefore, the oral dose of EOU was multiplied by 65% to convert to a dose comparable with the intravenous dose for the intention of equal drug bioavailability.

***Surgery, tumor******regression evaluation and adjuvant chemotherapy***

Radical surgery was performed 4 to 6 weeks after CRT completion. Primary tumor regression grade (TRG) was determined semiquantitatively according to a modiﬁed Dworak scale[34] based on the amount of viable tumor versus the amount of ﬁbrosis as follows: 0, no regression; 1, dominant tumor mass with obvious fibrosis and/or vasculopathy; 2, dominantly fibrotic changes with few tumor cells or groups (easy to find); 3, very few (difficult to find microscopically) tumor cells in fibrotic tissue with or without a mucous-like substance; and 4, no tumor cells and only fibrotic mass (total regression or response). A Dworak grade of 2 or 3 was determined by two experienced pathologists. CRT efficacy was classified as either a “good response” or a “poor response”. Good response cases were those whose tumor regression was classified as TRG 3 or 4; poor response cases were those whose tumor regression was graded as TRG 0, 1 or 2. Patients were advised to undergo four to six cycles of adjuvant chemotherapy that was the same as neoadjuvant chemotherapy 4 to 6 weeks after surgery completion. When patients could not endure the side effects of adjuvant chemotherapy, capecitabine monotherapy was adopted. Finally, 125 patients received 479 cycles of adjuvant chemotherapy.

***Follow-up***

After completion of combined treatment, patients were followed up every 3 to 6 mo in the ﬁrst 3 years and every 12 mo thereafter. Patient evaluation included a physical examination, abdominal ultrasonography or computed tomography scan, chest x-ray, and serum CEA and Ca19-9 levels. Diagnosis of recurrence was based on two types of radiologic examination with or without abnormal plasma tumor markers. Histopathological verification was performed when necessary. The survival status was veriﬁed by examination of clinical attendance records and direct telecommunication with the patient or their family in March 2016. Survival was censored at the time of the last follow-up on March 1, 2016, with a median follow-up time of 66 mo (range 17-99 mo).

***End points and statistical analysis***

The study end points were CRT efficacy, recurrence, disease-free survival (DFS) and overall survival (OS). DFS was defined as the interval from surgery to either confirmed recurrence or death, and OS was defined as the time interval between surgery and death.

Continuous variables were expressed as the mean ± standard deviation (SD). Student *t* test and chi-square tests were used to compare differences between groups. A receiver operating characteristic (ROC) curve was plotted to identify a proper cut-off value. Kaplan-Meier analysis was used to compare survival using the log-rank test. Univariate and multivariate Cox proportional hazard models were used to assess the effect of risk factors on survival. Forward conditional methods were used to build the multivariate Cox proportional hazards model. A two-tailed p-value less than 0.05 was considered statistically significant. Statistical analysis was performed with SPSS statistical software package (version 22).

**Results**

***Patient clinicopathological characteristics among different doses of******OME***

Among 63 OME users, 7 patients only received OME orally, 47 patients only received OME intravenously, and 9 patients received OME both orally and intravenously. The detailed information of OME dosage is presented in Table 1.The good response rate (50.8%) in the EOU was significantly increased compared with non-EOU (30.6%) (*p =* 0.02; OR = 2.336, 95%CI: 1.124-4.856). No signiﬁcant differences for other clinicopathological factors were found between the EOU and non-EOU groups (all *p*-values > 0.05). The patient characteristics of EOU and non-EOU are summarized in Table 2.

PPIs inhibit cancer cell proliferation in a dose-dependent manner[25,35]. Therefore, in addition to arbitrarily applying a cut-off that meets the inclusion criterion, a preferred OME dose cut-off for tumor recurrence was investigated by receiver operating characteristic (ROC) curves. The dose that was closest to the upper left corner (100% sensitivity and 100% speciﬁcity) was selected as the cut-off dose. The area under the ROC curve (AUC) was calculated to estimate the discriminatory power of the produced OME dose cut-off of the entire dose range on recurrence. A dose cut-off of 200 mg was identified by ROC as the optimized point that differentiated recurrence from non-recurrence with maximal sensitivity and speciﬁcity (Figure 1). The AUC was 0.66 (*p =* 0.053), and the OME dose of 200 mg differentiated recurrence from non-recurrence with a specificity of 82.4% and a sensitivity of 56.5%. Patients were then divided into the effective OME group (EOG, patients received OME ≥ 200 mg) and non-effective OME group (non-EOG, patients received OME < 200 mg). Non-EOG and EOG patient characteristics are summarized inTable 3.

The recurrence rate in EOG was 10.3% (3 out of 29), which is significantly lower than 31.3% (30 out of 96) in non-EOG (*p =* 0.025; OR = 0.25, 95%CI: 0.07-0.90, table 3). The response rate of CRT efficacy in EOG was 55.2% (16 out of 29), which was obviously increased compared with 36.5% (35 out of 96) in non-EOG, with a marginally significant difference (*p =* 0.072; OR = 2.15, 95%CI: 0.93-5.00, Table 3). There was no significant difference in other clinicopathological features between the non-EOG and EOG groups (all *p* > 0.05, Table 3). Non-EOG received a total of 371 cycles of adjuvant chemotherapy, with a mean value of 3.9 ± 2.2. EOG received 108 cycles, and the mean value was 3.7 ± 2.6. The mean adjuvant chemotherapy cycles between the EOG and non-EOG groups were not significantly different (*p* = 0.77).

***Survival between the non-EOG and EOG***

At the end of the study, 96 (76.8%) patients were still alive. The patients who did not survive all died of tumor-related death, and no patients died from PPI-related severe infection[36] during the CRT treatment period. The mean DFS and mean OS of all patients was 62.9 mo ± 25.5 mo, 95%CI: 58.4-67.4) and 66.6 mo ± 21.8 mo, 95%CI: 62.8-70.5), respectively. The 3- and 5-year DFS rates of all patients were 81.6% and 75.1%, respectively. The 3- and 5-year OS rates of all patients were 85.6% and 78.8%, respectively.

A significant difference in DFS was noted between non-EOG and EOG patients (*p =* 0.032, Figure 2A, Table 4). In addition, a marginally significant difference in OS was also observed (*p =* 0.092, Figure 2B, Table 4). BMI, ypTNM and CRT efficacy are significantly associated with DFS (*p =* 0.024, *p* ＜ 0.005 and *p =* 0.031, respectively, Table 4), whereas cTNM is a marginally significant factor of DFS (*p =* 0.067, Table 4). ypTNM is the only significant impact factor of OS (*p =* 0.003, Table 4), and BMI is a marginally significant factor of OS (*p =* 0.05, Table 4).

***Cox proportional hazards model analysis***

The univariate Cox analysis revealed that OME (non-EOG and EOG), BMI, CRT efficacy, and ypTNM are significantly associated with DFS (*p =* 0.044, 0.039, 0.036 and *p =* 0.006, respectively, Table 5). The cTNM was marginally significantly associated with DFS (*p =* 0.075, Table 5), and BMI was marginally significantly associated with OS (*p =* 0.069, Table 5). ypTNM was a significant impact factor for OS (*p =* 0.045). No other clinicopathological features significantly associated with DFS and OS (all *p* > 0.05, Table 5).

Furthermore, multivariate Cox analysis demonstrated that OME (non-EOG and EOG), BMI and ypTNM are independent and signiﬁcant predictors of DFS (*p =* 0.048, HR = 0.30, 95%CI: 0.09-0.99; *p =* 0.038, HR = 0.22, 95%CI: 0.05-0.92 and *p =* 0.01, HR = 1.58, 95%CI: 1.12-2.22). ypTNM was also an independent and signiﬁcant predictor of OS (*p =* 0.045, HR = 1.46, 95%CI: 1.01-2.11).

**Discussion**

Neoadjuvant CRT could greatly improve the anus save rate and decrease local recurrence rate in advanced rectal cancer management[2-4,37]. However, results addressing whether neoadjuvant CRT could improve survival are inconsistent[2,37]. The results of the present study showed that CRT efficacy is a significant clinicopathological factor associated with DFS (*p =* 0.031) and exhibits a favorable trend with OS (*p =* 0.144), indicating that CRT could decrease recurrence and potentially benefit OS. The results of the present study suggest that CRT efficacy is a significant clinicopathological factor associated with DFS, and this result is consistent with previous studies[2-4]. The present study results suggest that CRT has a potential benefit in OS but is not a significant predictor. These results were consistent with the study by R Sauer *et al*[37] but not the study of Calogero Cammà *et al*[2]. As a potential chemotherapeutic agent[27,38-42], PPIs are safe to humans at high doses and with long-term treatment[37,38]. The mechanisms by which PPIs affect cancer include inhibiting V-ATPase activity[17,18], inducing apoptosis[21-23], promoting autophagy[24,25] and stimulating caspase-dependent cell death[35]. PPIs could sensitize chemo-resistant tumors to cytotoxic drugs[26] and could improve the efficacy of T-cell-based cancer immunotherapy[27,28], suggesting that PPIs may improve cancer treatment efficacy. In the present study, we found a good response rate (50.8%) in the EOU group that was significantly increased compared with the non-EOU group (30.6%) (*p =* 0.02), suggesting that OME could enhance the sensitivity of rectal cancer to concurrent CRT. We noticed that after the OME dose cut-off was increased, the good response rate of CRT efficacy between EOG (55.2%) and non-EOG (36.5%) patients exhibited a marginally significant difference (*p =* 0.072). This result was likely caused by an elevated cut-off that resulted in a decreased EOG sample size, which would reduce statistical power. To the best of our knowledge, this study is the first to investigate the effect of PPIs on CRT efficacy.

Abnormal extracellular acidic pH could enhance the invasive capacity and metastatic behavior of cancer cells[43-46]. V-ATPase is involved in pH-dependent degradation of the extracellular matrix and promotion of tumor invasion and metastasis[39,47], suggesting that inhibition of V-ATPase may prevent metastasis. Consistent with these studies, the present study results showed that the recurrence rate in EOG patients was 10.3%, which was significantly reduced compared with 31.3% in non-EOG patients (*p =* 0.025). In addition, a significant difference in DFS was noted between non-EOG and EOG patients (*p =* 0.032), and a marginally significant difference in OS was noted (*p =* 0.092). Further multivariate Cox analysis demonstrated that OME (non-EOG and EOG) is an independent and signiﬁcant predictor of DFS (*p =* 0.048). These results suggest that when administered as an adjuvant chemoradiotherapy drug, OME may exert synergistic effects with concurrent CRT to reduce tumor recurrence.

Whether the plasma concentration of the including criteria dosage of OME in the present study could affect cancer cell vitality should be further discussed. The oral intake of 20 mg OME could produce a maximal plasma concentration of 2.5 mg/ml after two hours in patients[48]. The minimum OME dosage for the inclusion criteria in the present study was 40 mg intravenously administered, achieving a plasma concentration of 5 mg/ml. In *in vitro* studies, OME dissolved in normal saline at a concentration of 1 mg/mL induces apoptosis in B-cell cancers[22] and re-sensitizes drug-resistant cancer cell lines (22 melanomas, 2 colon adenocarcinomas, 2 breast cancers and 2 ovarian carcinomas) to cytotoxic drugs[26]. In *in vivo* studies, 0.4 mg/kg OME co-administered with dichloroacetate and tamoxifen exhibit a synergistically anti-proliferative effect on cholangiocarcinoma[49]. In addition, 2 mg/kg OME combined with dichloroacetate exhibited an antitumor effect on HT1080 fibrosarcoma cells inoculated in mice[50]. ESOM (2.5 mg/kg) reduced tumor growth in SCID mice engrafted with human melanoma[35]. In the present study, the minimum OME dose per kilogram of body weight was approximately 0.67 mg/kg (40 mg/60 kg), and the mean dose per kilogram of body weight was 3.6 mg/kg (217.2 mg/60.0 kg), which were higher than the least functional dosage reported above[49].

BMI was significantly associated with DFS (*p =* 0.024) and was a marginally significant factor associated with OS (*p =* 0.05). Further multivariate Cox analysis demonstrated that BMI was an independent and signiﬁcant predictor of DFS (*p =* 0.038), which was consistent with a previous study[51]. Our study has several limitations. Although consecutive patients were included, it is a retrospective study. In addition, the patient sample of the study was relatively small. However, the effects of OME on CRT efficacy, tumor recurrence and patient survival were first investigated in the present study, which would be helpful for randomized and controlled trials in the future.

When used as an adjuvant drug in cancer treatment, omeprazole has a synergetic effect on improving CRT efficacy and decreasing rectal cancer recurrence.

**comments**

***Background***

Abnormal pH gradients of tumor microenvironment are involved in tumorigenesis, tumor progression and drug resistance. Vacuolar type H+-ATPases (V-ATPases) are proton pumps expressed on the membrane of endolysosomal organelles and the plasma membrane, which could modulate the tumor acidic microenvironment. Proton pump inhibitors (PPIs), such as omeprazole (OME) and esomeprazole, are used to relieve common side effects of chemotherapy, such as nausea and emesis. In addition to targeting the gastric acid pump, PPIs inhibit the activity of V-ATPases. Moreover, PPIs induce apoptosis in multiple cancer cells and promotes cancer cell autophagy. PPIs also sensitize chemo-resistant tumors to cytotoxic drugs and improve the efficacy of T-cell-based cancer immunotherapy. These study results suggest that application of PPIs may be helpful to improve cancer treatment. However, whether PPIs affect CRT efficacy, reduce tumor recurrence and improve survival in rectal cancer remain unclear.

***Research frontiers***

The present study investigates whether omeprazole used as an adjuvant drug in cancer treatment could improve cancer treatment efficacy.

***Innovations and breakthroughs***

In contrast with previous *in vitro* and *in vivo* studies, the present study clinically revealed that when used as an adjuvant drug in cancer treatment, omeprazole has synergetic effects on improving CRT efficacy and reducing rectal cancer recurrence.

***Applications***

When used as an adjuvant drug in cancer treatment, omeprazole has a synergetic effect on improving CRT efficacy and reducing rectal cancer recurrence and is helpful in improving cancer treatment efficacy.

***Peer-review***

Zhang *et al* retrospectively reviewed a series of 125 patients with rectal cancer and demonstrated that omeprazole users had better prognosis in term of response and recurrence rates and disease-free survival.

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**Table 1 Mean dose and duration of omeprazole administered orally and intravenously**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **OME** | **Cases** | **administered dose (mg)** | | | |  | **number of days OME was administered** | | | |
| **mean ± SD** | **95%CI** | **max** | **min** |  | **mean ± SD** | **95%CI** | **max** | **min** |
| Oral1 | 7 | 260.0 ± 143.2 | 127.6-392.4 | 546 | 182 |  | 11.0 ± 8.0 | 3.6-18.3 | 28 | 7 |
| IV2 | 47 | 217.2 ± 184.8 | 162.8-271.3 | 940 | 40 |  | 3.8 ± 3.0 | 2.9-4.6 | 16 | 1 |
| IV+Oral3 | 9 | 406.2 ± 184.9 | 264.1-548.4 | 756 | 151 |  | 13.7 ± 7.0 | 8.2-19.1 | 28 | 7 |

1oral OME multiplied by 65%; 2OME received intravenously; 3oral OME multiplied by 65% plus OME received intravenously. OME: omeprazole.

**Table 2 Differences in the clinicopathological characteristics of patients between eligible omeprazole users and non-eligible omeprazole users**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Characteristics** | **Total** | **EOU** | | ***p*-value** | **Characteristics** | **Total** | **EOU** | | ***p*-value** |
| **Non** | **Yes** | **Non** | **Yes** |
| Sex |  |  |  |  | CA19-9 |  |  |  |  |
| male | 90 | 46 | 44 | 0.59 | <35 | 102 | 50 | 52 | 0.72 |
| female | 35 | 16 | 19 |  | ≥35 | 18 | 8 | 10 |  |
| Age(yr) |  |  |  |  | TGR |  |  |  |  |
| < 60 | 73 | 37 | 36 | 0.77 | 0 | 39 | 23 | 16 | 0.25 |
| ≥ 60 | 52 | 25 | 27 |  | 1 | 15 | 8 | 7 |  |
| BMI |  |  |  |  | 2 | 20 | 12 | 8 |  |
| < 25 | 100 | 47 | 53 | 0.25 | 3 | 24 | 9 | 15 |  |
| ≥ 25 | 25 | 15 | 10 |  | 4 | 27 | 10 | 17 |  |
| Tumor size(cm) |  |  |  |  | CRT efficacy |  |  |  |  |
| ≤ 3 | 49 | 24 | 25 | 0.95 | poor | 74 | 43 | 31 | 0.02 |
| 3-6 | 61 | 30 | 31 |  | good | 51 | 19 | 32 |  |
| ≥ 6 | 15 | 8 | 7 |  | ypTNM |  |  |  |  |
| Tumor grade |  |  |  |  | ypcr | 25 | 9 | 16 | 0.34 |
| 1 | 28 | 14 | 14 | 0.23 | Ⅰ | 26 | 16 | 10 |  |
| 2 | 88 | 46 | 42 |  | Ⅱ | 40 | 20 | 20 |  |
| 3 | 9 | 2 | 7 |  | Ⅲ | 34 | 17 | 17 |  |
| cTNM |  |  |  |  | Adjuvant CT |  |  |  |  |
| Ⅱ | 39 | 22 | 17 | 0.31 | non | 21 | 9 | 12 | 0.50 |
| Ⅲ | 86 | 40 | 46 |  | yes | 104 | 53 | 51 |  |
| CEA |  |  |  |  | Recurrence |  |  |  |  |
| < 5 | 62 | 28 | 34 | 0.47 | non | 92 | 46 | 46 | 0.66 |
| ≥ 5 | 58 | 30 | 28 |  | yes | 33 | 16 | 17 |  |

EOU: Eligible OME users; non-EOU: Non-eligible OME users; BMI: Body mass index; TGR: Tumor regression grade; adjuvant CT: Adjuvant chemotherapy.

**Table 3 Differences in clinicopathological characteristics of non-eligible omeprazole users and eligible omeprazole users patients**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Characteristics** | **Total** | **EOG** | | ***p*-value** | **Characteristics** | **Total** | **EOG** | | ***p*-value** |
| **Non** | **Yes** | **Non** | **Yes** |
| Sex |  |  |  |  | CA19-9 |  |  |  |  |
| male | 90 | 71 | 19 | 0.38 | <35 | 102 | 76 | 26 | 0.42 |
| female | 35 | 25 | 10 |  | ≥35 | 18 | 15 | 3 |  |
| Age(yr) |  |  |  |  | TGR |  |  |  |  |
| < 60 | 73 | 58 | 15 | 0.41 | 0 | 39 | 34 | 5 | 0.33 |
| ≥ 60 | 52 | 38 | 14 |  | 1 | 15 | 11 | 4 |  |
| BMI |  |  |  |  | 2 | 20 | 16 | 4 |  |
| < 25 | 100 | 77 | 23 | 0.92 | 3 | 24 | 17 | 7 |  |
| ≥ 25 | 25 | 19 | 4 |  | 4 | 27 | 18 | 9 |  |
| Tumor size(cm) |  |  |  |  | CRT efficacy |  |  |  |  |
| ≤ 3 | 49 | 37 | 12 | 0.94 | poor | 74 | 61 | 13 | 0.072 |
| 3-6 | 61 | 47 | 14 |  | good | 51 | 35 | 16 |  |
| ≥ 6 | 15 | 12 | 3 |  | ypTNM |  |  |  |  |
| Tumor grade |  |  |  |  | ypcr | 25 | 16 | 9 | 0.38 |
| 1 | 28 | 22 | 6 | 0.96 | Ⅰ | 26 | 21 | 5 |  |
| 2 | 88 | 67 | 21 |  | Ⅱ | 40 | 31 | 9 |  |
| 3 | 9 | 7 | 2 |  | Ⅲ | 34 | 28 | 6 |  |
| cTNM |  |  |  |  | Adjuvant CT |  |  |  |  |
| Ⅱ | 39 | 30 | 9 | 0.98 | non | 21 | 14 | 7 | 0.23 |
| Ⅲ | 86 | 66 | 20 |  | yes | 104 | 82 | 22 |  |
| CEA |  |  |  |  | Recurrence |  |  |  |  |
| < 5 | 62 | 45 | 17 | 0.39 | non | 97 | 66 | 26 | 0.025 |
| ≥ 5 | 58 | 46 | 12 |  | yes | 28 | 30 | 3 |  |

EOG: Effective OME group, non-EOG: Non-effective OME group; BMI: Body mass index; TGR: Tumor regression grade; adjuvant CT: Adjuvant chemotherapy.

**Table 4 Univariate analysis of impacts of various characteristics on survival**

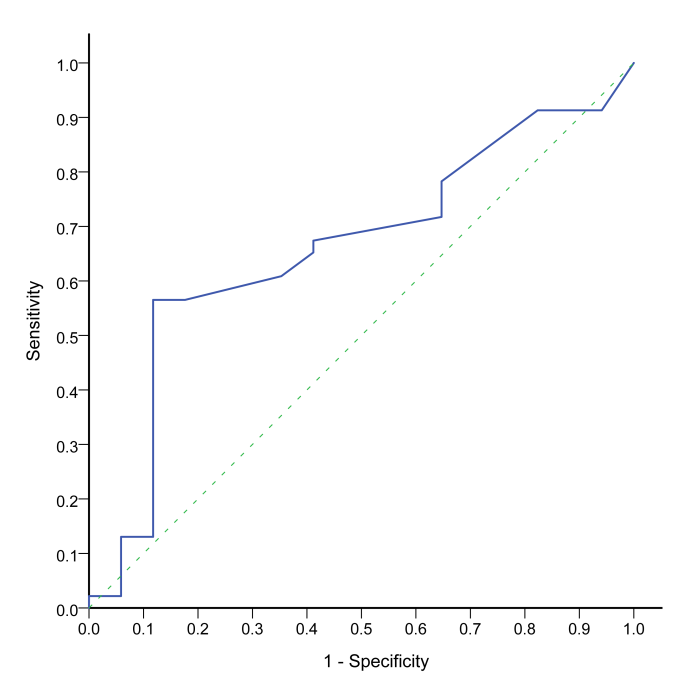
|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Characteristics** | **n** | **DFS** | | | ***p*-value** | **OS** | | | ***p*-value** |
| **mean(mo)** | **3-yr(%)** | **5 yr (%)** | **mean(mo)** | **3 yr(%)** | **5 yr(%)** |
| Sex |  |  |  |  |  |  |  |  |  |
| male | 90 | 61.8 ± 25.9 | 81.1 | 74.4 | 0.803 | 65.5 ± 22.2 | 84.4 | 79.9 | 0.855 |
| female | 35 | 65.6 ± 24.6 | 82.9 | 76.9 |  | 69.5 ± 20.1 | 88.6 | 79.8 |  |
| Age(yr) |  |  |  |  |  |  |  |  |  |
| < 60 | 73 | 63.3 ± 26.3 | 80.1 | 71.1 | 0.533 | 68.4 ± 22.0 | 86.3 | 80.7 | 0.908 |
| ≥ 60 | 52 | 62.4 ± 24.6 | 82.7 | 80.7 |  | 64.2 ± 21.5 | 84.6 | 78.7 |  |
| Tumor size(cm) | |  |  |  |  |  |  |  |  |
| ≤ 3 | 48 | 62.5 ± 26.1 | 81.2 | 77 | 0.571 | 65.0 ± 22.4 | 83.3 | 79.2 | 0.962 |
| > 3 | 77 | 63.2 ± 25.3 | 81.8 | 74 |  | 67.7 ± 21.6 | 87.0 | 80.3 |  |
| BMI1 |  |  |  |  |  |  |  |  |  |
| < 25 | 100 | 60.5 ± 26.8 | 77 | 69.9 | 0.024 | 65.3 ± 22.7 | 82 | 76.9 | 0.05 |
| ≥ 25 | 25 | 72.7 ± 16.6 | 96 | 96 |  | 72.1 ± 17.0 | 96 | 92 |  |
| Tumor grade |  |  |  |  |  |  |  |  |  |
| 1 | 28 | 64.7 ± 28.0 | 78.6 | 75 | 0.852 | 69.4 ± 22.5 | 85.7 | 78.6 | 0.931 |
| 2, 3 | 97 | 62.4 ± 25.0 | 82.5 | 75.2 |  | 65.6 ± 21.7 | 85.6 | 80.2 |  |
| cTNM |  |  |  |  |  |  |  |  |  |
| Ⅱ | 39 | 69.2 ± 23.2 | 87.2 | 84.6 | 0.067 | 71.9 ± 18.8 | 92.3 | 87.2 | 0.137 |
| Ⅲ | 86 | 60.0 ± 26.2 | 79.1 | 70.7 |  | 64.2 ± 22.8 | 82.6 | 76.4 |  |
| CEA |  |  |  |  |  |  |  |  |  |
| < 5 | 62 | 77.0 ± 4.1 | 69.2 | 69.2 | 0.789 | 79.6 ± 3.7 | 80.6 | 73.9 | 0.384 |
| ≥ 5 | 58 | 80.4 ± 4.3 | 82.8 | 74 |  | 86.1 ± 3.4 | 89.7 | 84.5 |  |
| CA19-9 |  |  |  |  |  |  |  |  |  |
| < 35 | 102 | 81.3 ± 3.1 | 83.3 | 75.4 | 0.174 | 84.2 ± 2.7 | 86.3 | 80.2 | 0.597 |
| ≥ 35 | 18 | 68.1 ± 9.2 | 72.2 | 66.7 |  | 78.3 ± 7.8 | 77.8 | 72.2 |  |
| CRT efficacy |  |  |  |  |  |  |  |  |  |
| poor | 74 | 60.7 ± 27.2 | 78.4 | 67.5 | 0.031 | 66.2 ± 23.2 | 83.8 | 75.6 | 0.144 |
| good | 51 | 66.1 ± 23.0 | 90.2 | 86 |  | 67.3 ± 19.9 | 88.2 | 86.1 |  |
| ypTNM |  |  |  |  |  |  |  |  |  |
| ypcr,Ⅰ,Ⅱ | 91 | 66.1 ± 24.0 | 85.7 | 82.3 | 0.005 | 68.5 ± 20.1 | 89 | 84.4 | 0.041 |
| Ⅲ | 34 | 54.3 ± 28.0 | 70.6 | 55.6 |  | 61.6 ± 25.5 | 76.5 | 67.6 |  |
| Adjuvant CT2 |  |  |  |  |  |  |  |  |  |
| non | 21 | 60.2 ± 31.5 | 71.4 | 71.4 | 0.385 | 63.5 ± 26.5 | 76.2 | 66.3 | 0.229 |
| yes | 104 | 63.5 ± 24.3 | 83.7 | 75.8 |  | 67.3 ± 20.8 | 87.5 | 82.7 |  |
| OME |  |  |  |  |  |  |  |  |  |
| non- EOU | 62 | 70.0 ± 25.8 | 85.5 | 75.6 | 0.658 | 73.9 ± 21.9 | 90.3 | 82 | 0.754 |
| EOU | 63 | 55.9 ± 23.5 | 77.8 | 74.6 |  | 59.5 ± 19.5 | 82.5 | 77.6 |  |
| OME (200 mg) |  |  |  |  |  |  |  |  |  |
| non-EOG | 96 | 62.0 ± 28.2 | 77.1 | 69.6 | 0.032 | 66.9 ± 24.1 | 82.3 | 76.9 | 0.092 |
| EOG | 29 | 65.9 ± 13.3 | 96.6 | 46.7 |  | 65.8 ± 12.0 | 96.6 | 89.5 |  |

1mean ± SD(mo); 2three or 5 years survival rate. EOU: Eligible OME users; non- EOU: Non-eligible OME users; EOG: Effective OME group; non-EOG: Non-effective OME group; BMI: Body mass index; TGR: Tumor regression grade; adjuvant CT: Adjuvant chemotherapy.

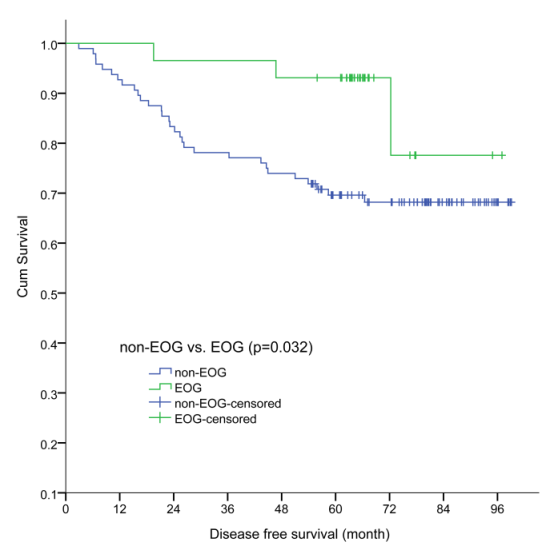
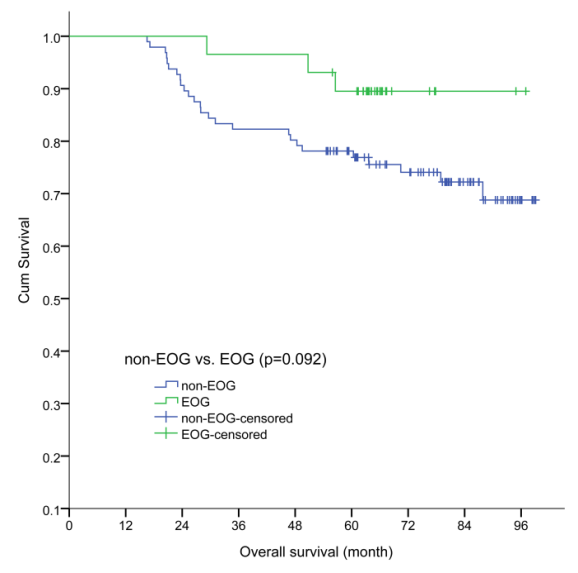
**Table 5 Univariate Cox analysis of the impacts of various characteristics on survival**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Characteristics** | **DFS** | | ***p*-value** |  | **OS** | | ***p*-value** |
| **HR** | **95%CI** |  | **HR** | **95%CI** |
| Sex |  |  |  |  |  |  |  |
| male *vs* female | 0.91 | 0.42-1.65 | 0.80 |  | 0.93 | 0.41-2.09 | 0.86 |
| Age |  |  |  |  |  |  |  |
| < 60 *vs* ≥ 60 | 0.8 | 0.40-1.62 | 0.53 |  | 1.05 | 0.50-2.19 | 0.91 |
| BMI |  |  |  |  |  |  |  |
| < 25 *vs* ≥ 25 | 0.22 | 0.05-0.93 | 0.039 |  | 0.26 | 0.06-1.11 | 0.069 |
| Tumor size |  |  |  |  |  |  |  |
| ≤ 3 *vs* ＞ 3 | 1.23 | 0.60-2.51 | 0.57 |  | 0.98 | 0.46-2.08 | 0.96 |
| Tumor grade |  |  |  |  |  |  |  |
| 1 *vs* 2,3 | 1.08 | 0.47-2.50 | 0.85 |  | 0.96 | 0.41-2.26 | 0.93 |
| cTNM |  |  |  |  |  |  |  |
| Ⅱ*vs* Ⅲ | 2.23 | 0.92-5.41 | 0.075 |  | 1.96 | 0.80-4.80 | 0.144 |
| CEA |  |  |  |  |  |  |  |
| < 5 *vs* ≥ 5 | 0.91 | 0.46-1.81 | 0.79 |  | 0.72 | 0.34-1.51 | 0.39 |
| CA199 |  |  |  |  |  |  |  |
| ＜ 35 *vs* ≥ 35 | 1.77 | 0.77-4.08 | 0.18 |  | 1.3 | 0.50-3.40 | 0.6 |
| CRT efficacy |  |  |  |  |  |  |  |
| 0,1,2 *vs* 3,4 | 0.43 | 0.19-0.95 | 0.036 |  | 0.55 | 0.24-1.24 | 0.15 |
| ypTNM |  |  |  |  |  |  |  |
| ypcr,Ⅰ,Ⅱ *vs* Ⅲ | 1.61 | 1.14-2.27 | 0.006 |  | 1.46 | 1.01-2.11 | 0.045 |
| Adjuvant CTb |  |  |  |  |  |  |  |
| non *vs* yes | 0.69 | 0.30-1.60 | 0.39 |  | 0.60 | 0.25-1.40 | 0.24 |
| EOU |  |  |  |  |  |  |  |
| non *vs* yes | 1.17 | 0.59-2.31 | 0.66 |  | 1.13 | 0.54-2.37 | 0.75 |
| EOG |  |  |  |  |  |  |  |
| non *vs* yes | 0.300 | 0.90-0.97 | 0.044 |  | 0.37 | 0.11-1.23 | 0.11 |

EOU: Eligible OME users; non- EOU: Non-eligible OME users; EOG: Effective OME group; non-EOG: Non-effective OME group; BMI: Body mass index; TGR: Tumor regression grade; adjuvant CT: Adjuvant chemotherapy.



**Figure 1 receiver operating characteristic curve of omeprazole dose for recurrence.**

A B

**Figure 2 Disease-free survival curves (A) or OS curves (b) of non-omeprazole and omeprazole.** EOG: Effective omeprazole.