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Advances in Multidisciplinary Treatment of Rectal Cancer

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ABSTRACT To summarize the advances in the multidisciplinary treatment of rectal cancer and to analyze the existing problems and development prospects. The full text database retrieval system of MEDLINE and the periodicals of CHKD were searched. The words "rectal cancer, diagnosis, surgery, chemotherapy, radiotherapy, targeted therapy, analysis" were used as key words for retrieval of literature concerning the values and clinical significance of rectal cancer multidisciplinary treatment from January, 2000 to December, 2007. Thirty papers were selected, of which 26 were used in analysis at last. Accurate preoperative staging of rectal cancer is a key factor in the multidisciplinary and comprehensive treatment of patients. A new therapy which is combined with radical operation can reduce the rate of local recurrence, prolong survival time, and particularly, promote the rate of sphincter preservation. Radical surgery combined with adjuvant therapy is still recognized as standard treatment modality for the patients with rectal cancer in stage II-III. Total removal of resectable metastases followed by prompt standard adjuvant therapy may extend survival time. The introduction of new chemical drugs, drugs of targeting therapy, and a regimen of combination therapy may improve outcomes in treatment for rectal cancer patients. A treatment standard for rectal cancer patients needs to be actively pursued. Compared with colon cancer patients, there has not been sufficient evidence to confirm that the total survival rate of rectal cancer patients after multidisciplinary and comprehensive treatments has been improved; therefore, it needs to be further studied.

KEY WORDS: rectal cancer, surgery, chemotherapy, radiotherapy, analysis.

Introduction

Rectal cancer is one of the common malignant tumors both in China and the rest of the world. The incidence of rectal cancer has increased in recent years, what is more, the treatment efficacy of rectal cancer has been unsatisfactory for the past 30 years. The American Cancer Society found that after analyzing 25,000 cases of colorectal cancer, the 5-year survival rate of rectal cancer patients was 50%. The Clinical Research Center of Oxford University in England analyzed 32,000 cases of colorectal cancer over the world and found that 3-year and 5-year survival rates of rectal cancer patients were 65% and 45.1%, respectively[1,2]. So far, a number of reports concerning rectal cancer cases showed that the 5-year survival rate was around 50% after surgery and found that local recurrence and distant metas-

tases were the main reasons for treatment failure. Therefore, developing multidisciplinary and comprehensive treatment for rectal cancer patients, reducing the rate of local recurrence and distant metastases as well as improving the patients' DFS (disease-free survival) are the goals of research in rectal cancer patients. This article summarized the progress in multidisciplinary treatment of rectal cancer in recent years.

Median and inferior segment of rectal cancer is the focus of research

The rectum is the portion of the large intestine which ends at 15 cm above the anal margin, based on the traditional anatomy. According to tumor site, it is divided as follows. In inferior segment rectal cancer, the tumor is located at less than 7cm above the anal verge. In median rectal cancer, the tumor is located at 7 cm-10 cm above the anal verge, and in upper rectal cancer, the tumor is located at more than 10 cm above the anal verge. However, in recent years, one view is that the rectum is the portion of large intestine which ends at 12 cm above the anal verge[3,4]. The theory is based on the following. According to the anatomy, the segment of large intestine > 12 cm above the anal verge has the characteristics of the colon, which has liberation mesentery. According to biology, the rule of recurrence in cancer of the large intestine > 12 cm is similar to colon cancer. In therapy, the treatment of upper rectal cancer located near the upper portion of the peritoneal reflexion is similar to colon cancer. Because of the special anatomic structure and blood supply as well as the special location of the tumor, the operative area is minimal, which makes the surgery more difficult than removing the tumor located at upper rectum. Although total mesorectal excision (TME) has improved the survival rate in recent years, the local recurrence rate in inferior segment rectal cancer is 3-5 times of that in the upper segment, and the prognosis is worse. Rectal cancer located in the median and inferior segments is the focus of current research. Some clinical trials have been involved in new adjuvant radiotherapy treating rectal cancer located at 16 cm above the anal verge[5]. This may include that the patients with tumors located in the upper peritoneal reflexion have received radiotherapy which is not necessary, therefore, the radiotherapy is regarded as an excessive treatment. The other converse situation is that, the conservative clinical trials have confined the new adjuvant radiotherapy to rectal cancer located at 12 cm above the anal verge[3,4]. Regarding upper segment T_3N_0 rectal cancer, with better prognostic features, including a recurrence rate < 10%, negative lymph nodes, accurately identified as N0 by examination of a minimum of 12 lymph nodes, negative resection margin and negative vascular invasion, the benefit of excessive radiotherapy may be limited, therefore, chemotherapy could be used as a substitution.

Importance of staging

Accurate staging is a premise in applying multidisciplinary and comprehensive treatment. However, according to the reports in the literature, the accurate rate of diagnosis of rectal cancer done by clinical doctors through rectal digital examination was only 67.5%−83%. Before initiating treatment, accurate staging in rectal cancer patients needs to be confirmed, as it is an important factor in deciding the modality of the treatment. In recent years, the application of imaging technology has improved the accuracy of TN staging. *i*) MRI can display the level of intestinal wall clearly, and the accuracy of T staging is 66%−92%[3,6]. After the new adjuvant radiotherapy, it is difficult for intrarectal MRI to identify the difference between radiation fibrosis and tumor invasion, therefore, it has limited use in staging. *ii*) EUS (endoscopic ultrasonography) is more accurate than other methods in T and N staging of rectal cancer before surgical resection [3,7]. A recent study analyzed 4118 cases of rectal cancer, and found the accurate rate of diagnosis by EUS was 85% and 75% for T and N staging, respectively. *iii*) TRUS (transrectal ultrasound) can supply important information for T and N staging in rectal cancer. For intestinal lymph nodes with a diameter > 10 mm, and the positive rate of the examination is 67.9%, but the tumor with incarcerated mesocaval or located in the upper rectum may affect the accurate result of staging by EUS and TRUS[8]. *iv*) Utilizing virtual computer imaging (indigo carmine) pigment endoscope technology, Hurlstone et al.[9] reported that, with low and high power mode, accurate rates of diagnosis of ancipital type or depressed rectal cancer were 83% and 90%, which is obviously higher than those by traditional colonoscopy. *v*) PL (pelvic lymphoscintigraphy) is a better way to evaluate lymph node metastases currently, because the accurate diagnosis rate of intestinal lymph nodes is 76%. *vi*) PET/CT is not recommended conventionally because there were more limitations in T and N staging of rectal cancer preoperatively.

New adjuvant treatment patterns and focus of discussion

New adjuvant therapy is a preoperative treatment, and includes new adjuvant radiotherapy, new adjuvant chemotherapy and new adjuvant chemoradiotherapy (CRT). In recent years, new adjuvant therapy has been used for treating patients whose tumor is located at the median or inferior segment of the rectum more and more, in particular, for treating local progression stages (T_3-T_4) or metastatic mesorectal lymph nodes in median and inferior segment rectal cancer (II-III). The goals of the new adjuvant therapy is to reduce tumor size and improve stage, even to completely eliminate the tumor, to increase the rate of root excision obviously (R0), to

increase the sphincter preservation rate, to reduce the rate of local recurrence and to improve the postoperative survival rate[10,11]. The American Cancer Center recommends the new adjuvant therapy as a standard therapy in rectal cancer treatment[12].

New adjuvant radiotherapy

New adjuvant radiotherapy is the focus of recent research. At present, new adjuvant radiotherapy is more effective than adjuvant radiotherapy, which plays an important role in enhancing the chance of sphincter preservation for patients with the median and inferior segment rectal cancer during surgery. New adjuvant radiotherapy recommends high doses of conventional fractionated radiotherapy, of which total dose is 45-50.4 Gy, 1.8 Gy each time，25-28 times, 5 times each week, lasting about 5 weeks for a cycle[13]. For resectable cancer, after 45 Gy of irradiation, a boost to the tumor bed with a 2 cm margin off the tumor is irradiated with 5.4 Gy in 3 fractions before surgery. The limited dosage of radiation to the small bowel is no more than 45 Gy and synchronously, the chemotherapy is given. Surgery should be considered 4-6 weeks after radiation. Recently, a randomized trial in France which compared the interval of 6-8 weeks with that of 2 weeks after the new adjuvant radiotherapy proved that surgery given 5-6 weeks after the new adjuvant radiotherapy has the advantage of improving the rate of the anus preservation (72% *vs.* 53%, $P = 0.007$) for the patients whose rectal cancer is located within 5 cm above the anal verge, and the preservation rate of anus was 38% and 23%, respectively. In recent years, the authors of studies in the Netherlands determined the efficacy of new adjuvant radiotherapy + TME after follow up of patients for 2 years. The analytical results showed that the 2-year rate of local lose of control in the patients in stage III with negative margin, who received TME is 15%, and that in the same kind of patients who received new adjuvant radiotherapy + TME is 4% ($P < 0.001$), therefore, the rectal cancer patients in stage III benefit more from the new adjuvant radiotherapy.

The value of new adjuvant chemoradiotherapy

Chemotherapy combined with radiotherapy, can reach synergies. The use of the 5-FU chemotherapy regimen enhances the effect of radiation, and radiation therapy can increase the activity of thymidine phosphorylase in the tumor cell, which enhances the role of 5-FU[14]. Currently, it is believed that new adjuvant chemoradiotherapy is one of the most important treatments for T_4 (or) N+ median and inferior segment of rectal cancer and anal cancer. New adjuvant chemoradiotherapy can provide an opportunity for radical excision of local and late stage of rectal cancer[10,11]. The application of new adjuvant chemoradiotherapy can improve local control, and, at the same time, further enhance the root excision rate and the anus preservation rate[3]. In addition, the followings can benefit from new adjuvant chemoradiotherapy. *i*) Larger tumors that are fixed or obstructed in median and inferior segment rectal cancer. *ii*) Tumors where imaging indicates stage T3-T4. *iii*) When violation of the bladder, prostate, cervix, the posterior wall of the vagina or of the anus exist. *iv*) If there is mesorectal or pelvic lymph node metastasis. *v*) If the tumor is poorly differentiated, but no distant metastasis of the tumor are located at the median and inferior segment of the rectum. Although the overall survival time (OS) is not significantly improved, a large-scale phase III clinical study showed that new adjuvant chemoradiotherapy had a better control rate of local tumor than the adjuvant chemoradiotherapy, and 10%-25% of the patients can achieve pathologically complete remission[11]. A phase III clinical study from Germany, comparing the difference in efficacy between new adjuvant chemoradiotherapy and adjuvant chemoradiotherapy in rectal cancer, confirmed that the local recurrence rate (6%) of patients treated with the new adjuvant chemoradiotherapy is lower than that with adjuvant chemoradiotherapy (13%) ($P = 0.006$). The rate of lymph node metastasis in patients with new adjuvant chemoradiotherapy is 20%, and that of patients with adjuvant chemoradiotherapy is 40% ($P < 0.001$). In patients with anal preservation, 45/116 (39%) of the patients received the new adjuvant chemoradiotherapy, and 15/78 (19%, $P= 0.004$) received the adjuvant chemoradiotherapy. Therefore, most cancer centers recommend the new adjuvant chemoradiotherapy as the multidisciplinary and comprehensive measure in rectal cancer treatment. Further, the new adjuvant chemoradiotherapy does not increase the surgical complications[6,10]. At present, 5-FU, capecitabine, oxaliplatin,and irinotecan, are the main chemotherapy drugs. The new adjuvant chemoradiotherapy regimen includes 5-FU/LV, FOLFOX (5-FU/LV+oxaliplatin), FOLFIRI (5-FU/LV+ irinotecan) and capecitabine single regimen. Andre et al. [14] considered the FOLFOX regimen superior to the FOLFIRI regimen. FOLFOX4, 6 is usually used as the first-line treatment regimen, and the FOLFIRI regimen is the second-line treatment[15]. When these regimens are combined with new adjuvant therapy, it is also known as the intensified neoadjuvant chemoradiotherapy, which can improve the complete remission rate from 9%-29% to 19%-37%[10].

The treatment of complete pathologic response

There were some disputes on how to treat the patients that achieved the complete remission based on the pathology [10,11]. Some researchers suggested that these patients could be closely observed or could receive local excision, while others still recommend the root resection after receiving the new adjuvant chemoradiotherapy. The focus of the dispute is that there is not a good way to determine whether the patients really achieve complete remission on the pathology or not, and particularly,

if it can be determined if the lymph node micrometastases in the mesorectum had existed. Many studies have reported that there were still 16%-18% of the patients with lymph node metastases. Therefore, it was suggested that as the accurate staging and sufficient evidence of complete remission of the patients were absent, the only close observation or local resection be performed. For the patients with sphincter invasion before therapy, complete remission can be achieved after new adjuvant chemoradiotherapy, but sphincter-saving resection is not suitable. The 2008 version of NCCN (National Comprehensive Cancer Network) Rectal Cancer Clinical Practice Guidelines (Chinese version) recommends an interval of 5-10 weeks following completion of full dose of neoadjuvant chemoradiotherapy lasting for 5.5 weeks prior to operation.

Some problems in surgical treatment

The difficulties of transabdominal resection

There are difficulties presented in the following aspects during the transabdominal resection of the tumor: sphincter preservation, bladder and sexual dysfunction, and local recurrence rate. In the past, median and inferior segment rectal cancer accounted for 70% of rectal cancers, however, in recent years, the proportion of median and upper segment rectal cancer is improving. At present, nearly 80% of rectal cancer surgery is sphincter-saving procedure, while the distance of distal margins is also the focus in the operation. The 2008 version of NCCN (National Comprehensive Cancer Network) Rectal Cancer Clinical Practice Guidelines (Chinese version) recommends that it is acceptable to remove the distal anal duct 1-2 cm for inferior rectal cancer (< 5 cm from anus verge), which needs congealing pathological examination to ensure negative margins of the sample in the operation. After liberating the total rectum, the surgeon has to ensure negative distal margins and to remove enough mesorectum. A positive radial margin means that the tumor is less than 1 mm or 2 mm from the resection margin. In the Netherlands, a group of researches showed that when the radial margin is less than 1 mm, the local recurrence rate is 38%, when that is less than 2 mm, the local recurrence rate is 16%, and when that is more than 2 mm, the local recurrence rate is only 6%. There is a clear definition of space in front of and behind the rectum, so TME can reduce the rate of positive circumferential margins. It is noteworthy that because the ligamentum laterale does not have an obvious interspace and is also the main pathway of an autonomic nerve, removal of the ligamentum laterale invaded by tumor is recommended in order to ensure a negative circumferential margin, and to preserve the autonomic nerve nearby the ligamentum laterale simultaneously.

TME and adjuvant treatment

The concept of TME including: *i*) total mesorectal excision at 4-5 cm below the distal edge of the tumor for an adequate mesorectal excision, no matter how far the tumor is from the anal verge, *ii*) emphasis on removing the circumferential margin, *iii*) reducing the rectal distal margin 0.5 cm, *iv*) preservation of the pelvic autonomic nerve, *v*) preservation of sphincter function- the rate of maintaining the sphincter function is 90% in anterior resection. Currently, TME has become the standard surgical approach, advocating the complete removal of the tumor with the remaining end wrapped using the pelvic fascia splanchnopleure, scavenging metastatic lymph nodes, and synchronously removing the mesorectum to the levator ani muscle to 4-5 cm below distal edge of tumor and preserving the autonomic nerve. Research from many countries indicates that TME can reduce the rate of local recurrence in rectal cancer to 2.2%-7.3%. Whether the patients need adjuvant chemotherapy or not after TME is still controversial. Some researchers suggest that 4-month adjuvant chemotherapy after TME is acceptable.

The improvement and significance of lymph node dissection methods

For the patients opting for root resection, the 5-year survival rate is relevant to TN staging directly. In the patients with stage I ($T_{1-2}N_0$), stage IIA (T_2N_0), stage IIB (T_4N_0), stage IIIA ($T_{1-2}N_0$), stage IIIB ($T_{3-4}N_0$), stage IIIC (N_2), the 5-year survival rate is 93%, 85%, 72%, 83%, 64%, 44%, respectively. Thus, the number of lymph node biopsied during surgery in rectal cancer and the lymph node-positive rate are very important indications in the staging and in choosing the adjuvant treatment regimen. Lymph node dissection in rectal cancer mainly includes upper, lateral, inferior to the rectal tumor. *i*) The anodic lymph node metastases are the most important in regards to direction of lymphatic drainage in rectal cancer. Lymph nodes around the inferior mesenteric artery root is the end in the anodic dissection. *ii*) Most scholars believe that lateral lymph node dissection should not be carried out routinely. The basis is that the rate of lateral lymph node dissection is low (< 10%). *iii*) The inferior lymph node dissection in rectal cancer is that the dentate line is the limit. The anodic lymph node drains to the anodic mainly, and the inferior lymph node drains to the inferior mainly. For the tumor invading the anal canal that appears to have inguinal lymph node metastases, we can carry out root resection and inguinal lymph node dissection simultaneously. Another way is to carry out the root resection and inguinal lymph node dissection completely, and to biopsy or remove the clinically suspicious nodes beyond the field of resection if possible. Extended resection is not indicated in the absence of clinically suspected nodes. The AJCC and College of American Pathologists (CAP) recommend evaluation of a minimum of 12 lymph nodes to accurately identify stage II rectal cancers[16]. The NCCN Treatment Center detected lymph nodes after radical resection in the years

of 2005-2006 and divided them into ≥ 12 lymph nodes group and < 12 lymph nodes group, and then compared the 2 groups. The results showed that the ≥ 12 lymph node group increased the lymph node-positive rate and N staging. Therefore, pathological examination of 12 lymph nodes postoperatively is recommended as a gold standard in pN0 diagnosis[17]. There is no consensus as to the examination of the sentinel lymph node by immunohistochemistry (IHC) and/or histological investigation to detect the presence of micrometastases. Some scholars believe that tumor foci that show evidence of growth (e.g., glandular differentiation, distension of sinus, or stromal reaction) should be diagnosed as lymph node metastases regardless of size[18]. However, at present, the use of sentinel lymph nodes and the detection of ITC (isolated cancer cells) by IHC alone has remained in the research phase, and therefore, the results in clinical management decisions need to be used with caution.

Local excision

For the early rectal cancer confined within the submucosua (T_1 N_0M_0), not accompanied by high risk of recurrence, the local resection may achieve the same effect as the radical treatment. The 2008 version of NCCN Rectal Cancer Clinical Practice Guidelines (Chinese version) recommended the criteria by transanal excision including: ①< 30% circumference of bowel, ②< 2.5 cm in size, ③ negative margin (> 3 mm), ④ mobile, non-fixed, ⑤ within 8 cm of anal verge, ⑥ endoscopically removed polyp with cancer or indeterminate pathology, ⑦no lymphovascular (LVI) or perineural invasion, ⑧ T_1, well to moderately differentiated, no evidence of lymphadenopathy on pretreatment imaging. Local excision includes: transsacral or transanal local excision, TEM (transanal endoscopic microsurgery). It is still controversial for TEM in clinical value. The reasons are: *i*) the accuracy of endorectal MRI and EUS, TRUS for stenosal enteric cavity or upper rectal cancer reduced significantly in preoperative TN staging, *ii*) TEM lacking regional lymph node resection or sampling. Recently, 4 retrospective studies have shown that the local recurrence rate of the local excision group is superior to that of the root excision group, and the difference of 5-year survival rate between the two is 8%-12%. After T1 tumor local excision, 10-year local recurrence rate is as high as 17%, even if combined with adjuvant radiotherapy. It can only delay the local recurrence, cannot reduce the local recurrence rate, and the efficacy was significantly lower than transabdominal resection[19]. For the patients with T_1N_0 in rectal cancer, Madbouly reported that the 5-year local recurrence rate is as high as 29.4% after local excision, in which 50% of them may have the chance to receive salvage resection of the root, and the 5-year survival rate is only 75%[20]. Therefore, local excision should be chosen cautiously. Local excision is restricted to the older patients corresponding to the standard of transanal resection or to the patients with other severe complications unsuited for transabdominal root excision. The patients with T_1 should be followed up 5 years or even longer after local excision. The patients who are still > T_2 after therapy, should undertake TME. For any patient with T and N, M_1 resectable tumor and synchronous metastases, the criteria in the treatment should be to remove the resectable tumor and metastatic tumor as soon as possible. The resection of metastatic and primary tumors synchronously or metachronously need to be followed by adjuvant therapy so as to extend survival time.

Adjuvant therapy

Adjuvant radiotherapy

Indications for adjuvant radiotherapy[6] are as follows. *i*) For the patients without neoadjuvant radiotherapy, T_3-T_4 and (or) N+ of median and inferior segment rectal cancer and anal canal cancer, the radiation therapy field should include the tumor or tumor bed, with a 2-5 cm margin, the presacral nodes, and the internal iliac nodes. The external iliac nodes should also be included for T4 tumors involving anterior structures, and the inguinal nodes for tumors invading into the distal anal canal. For postoperative patients undergoing abdominalperineal resection, the perineal wound should be included within the fields. *ii*) The patients with T_3 N_0 rectal cancer in the inferior segment receiving no new adjuvant radiotherapy have high risk factors (poorly differentiated pathology, circumferential resection margin < 2 mm, violation of vascular integrity, the number of examined lymph nodes < 12). *iii*) For the patients with high risk of pelvic recurrence, the radiation dose is 40-50 Gy in 25-28 fractions to the pelvis. Palliative radiotherapy is mainly used for: *i*) patients with locally advanced unresectable rectal cancer, *ii*) patients with distant metastases or recurrence. Adjuvant radiotherapy or adjuvant chemoradiotherapy has become an important part of multidisciplinary and comprehensive treatment in rectal cancer treatment. Although TME reduces the local recurrence rate significantly for the postoperative patients, currently, it is generally acknowledged that TME combined with adjuvant radiotherapy or chemoradiotherapy can further reduce the local recurrence rate and improve DFS (disease-free survival rate). Results of the trial done by the American Gastrointestinal Cancer Study Group showed that compared with surgery alone, adjuvant radiotherapy can improve local control rate. Adjuvant chemoradiotherapy is better in improving the local control rate, and significantly so in improving DFS (disease-free survival rate). A multi-center study led by Mayo showed that adjuvant chemoradiotherapy can significantly reduce distant metastases (P = 0.011) and improve OS (overall survival) (P = 0.025).

The value of adjuvant chemotherapy and adjuvant chemoradiotherapy

The modality and efficacy of the adjuvant chemotherapy for rectal cancer patients has been controversial. The 2008 version of NCCN Rectal Cancer Clinical Practice Guidelines (Chinese version) obviously recommends that the rectal cancer patients with pT_3, N_0M_0 or pT_{1-3}, N_{1-2}, any T, N_{1-2}, pT_{1-2}, N_X or with any high risk factors (poor differentiation, vascular invasion, positive margins, uncertain lymph node detection) should receive adjuvant chemotherapy after transabdominal resection[21]. Quasar II trial results showed that 5-FU/LV-based adjuvant chemotherapy after surgery had obvious survival advantage for patients with stage II rectal cancer[22] .The United States has approved FOLFIRI as the standard regimen for the patients with advanced colorectal cancer. It recommended that for the patients with progressive rectal cancer, 5-FU/LV-based, infusional 5-FU plus oxaliplatin formulate FOLFOX regimen, or 5-FU plus irinotecan formulate FOLFIRI regimen. FOLFOX and FOLFIRI are interoperable as first-line or second-line chemotherapy regimen. de Gramont et al.[23] compared FOLFOX4 with 5-FU/LV and found that the efficacies were 50% and 22%, respectively. Further, it showed the median PFS (progression-free survival period) was 9 months and 6.2 months and that the outcome in FOLFOX4 group was superior to that in 5-FU/LV group. Wolmark et al.[24] reported that 700 cases with rectal cancer using adjuvant chemotherapy (5-FU/LV) or adjuvant chemoradiotherapy (50.4 Gy) for 6 months showed that the chemoradiotherapy reduced local recurrence rate. Recently, Dobie et al.[25] analyzed clinical data of 2886 cases with rectal cancer in stage II-III, in which 45.4% utilized adjuvant chemoradiotherapy. In the patients with stage III opting for adjuvant treatment, 68.2% of the patients accepted adjuvant chemotherapy, and 96.6% accepted radiotherapy. Comparing the outcomes of these patients with that of the patients not receiving adjuvant treatment, the 5-year death rate was decreased in the patients with stage III rectal cancer who received adjuvant chemoradiotherapy. The overall principle in the treatment of rectal cancer patients is to receive adjuvant chemoradiation therapy as early as possible. The patients, after receiving abdominalperineal resection, may have slower perineal wound healing, and, therefore, may receive chemoradiation therapy after 2 courses of chemotherapy. For the patients with low anterior resection, chemoradiation therapy should begin 4 weeks following the surgery[26].

Adjuvant chemotherapy combined with targeted drug in advanced rectal cancer

For advanced rectal cancer patients receiving the optimal supportive therapy, their median life expectancy is less than 6 months. For the patients receiving 5-FU/LV, it may be extended to 10-12 months, while with oxaliplatin or irinotecan combined with 5-FU/LV, it may be extended to 14-20 months. In the 2007 ASCO meeting, the EPIC trial proved that the use of 5-FU/LV or capecitabine combined with oxaliplatin or irinotecan, then with the addition of cetuximab, can extend the median overall survival to more than 33 months. Cetuximab had been approved as a second-line and third-line drug to treat recurrent or metastatic rectal cancer, and the efficacy of cetuximab alone was about 12%. Cetuximab can reverse the tolerance of oxaliplatin or irinotecan, and its curative effect was irrelevant to the expression of EGFR (epidermal growth factor receptor). Cetuximab in combination with FOLFIRI or FOLFOX regimen, can lead to 64.6% of the overall efficacy rate , and the toxicity was not superimposed. Currently, there is no evidence to support the application of panitumumab after cetuximab failure, or the application of cetuximab after panitumumab failure. Panitumumab combined with chemotherapy is not supported either[27]. The 2008 version of NCCN Rectal Cancer Clinical Practice Guidelines (Chinese version) recommended oxaliplatin plus bevacizumab, or irinotecan plus bevacizumab.

Conclusion

In short, the introduction of a multidisciplinary treatment mode can reduce local recurrence rate and improve DFS (disease- free survival) for the rectal cancer patients, but for the improvement of overall survival (OS) time, it is still unsatisfactory. Therefore, it is very important to find the ways to discover primary micrometastases and prevent local recurrence as well as distant metastases effectively.

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