

Original Article

Treatment Benefit Analysis for Patients Older Than 80 Years of Age with Clinical Stage II or III Rectal Cancer

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Key Words

Rectal cancer;
Elderly patient

Background and purpose. The incidence of colorectal cancer increases with age and treatment of rectal cancer includes surgical resection, total mesorectal excision, chemotherapy, and radiotherapy. However, old age is an important risk for all treatment and has higher rates of comorbidity and mortality. Moreover, those older patients will also encounter other severe disease in their remaining life besides cancer. In this article, we investigate the outcome of patients older than 80-year-old and analyze that survival benefit of treatment.

Methods. We retrospectively reviewed the medical records of patients in our section of Taipei Tzu Chi Hospital who was diagnosed as clinical stage II or III rectal cancer from 2007 to 2015. We compared and analyzed the patients' clinical characteristics, treatment choice, outcome, and death etiology.

Results. 29 cases were diagnosed as clinical stage II or III histologically-confirmed rectal cancer. 18 of 29 patients were between 80~84 years of age, 8 were between 85~90 years old, and 3 patients were older than 90 years. 55% of patients had more than two systemic comorbid illnesses. 75% patients died during follow-up. Of those patients who died, 57.1% had deaths recorded as being due to their cancer. multivariate cox regression analysis demonstrates that only adjuvant chemotherapy has survival benefit.

Conclusions. We conclude that the administration of oral chemotherapy is feasible and has survival benefit in patients older than 80-year-old with clinical stage II or III rectal cancer.

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Colorectal cancer (CRC) is the most frequent cause of new cancer diagnosis in Taiwan with 15,140 new cases and approximately 5,265 deaths due to CRC reported in Taiwan in 2013. The incidence of CRC increases with age and occurs most commonly in patients who are 70~79 years old. In addition, mortality rates increase with age with the highest incidence

in those patients who are > 85 years of age.

Rectal cancer occurs in approximately 30% of all patients with CRC.¹ Treatment of rectal cancer includes surgical resection, total mesorectal excision (TME), chemotherapy, and radiotherapy. Based on NCCN guidelines, the preferred treatment of rectal adenocarcinoma at a stage > T3N0 includes all three types of treatment.

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Advanced age and comorbidities limit the choice of treatment. For example, FOLFOX is less frequently prescribed in patients older than 80 years of age and TME for middle to low rectal cancer in the elderly is considered high risk surgery.

Patients older than 80 years of age are in a different treatment class compared with younger patients. Previous research has demonstrated higher rates of comorbidity and higher postoperative 30-day mortality rates for patients older than 80 years of age.² For patients using oral tagafur/leucovorin, adjuvant oral chemotherapy may improve survival and reduce distant relapse compared with surgery alone.³ However, elderly patients may stop using oral chemotherapy or require reduced doses, due to frequent side effects such as weakness and infection. These interruptions and/or reductions in dosage may decrease the effectiveness of the chemotherapy. In this article, we investigate the outcome of patients older than 80-year-old and analyze that benefit of treatment.

Materials and Methods

This study was approved by the Institutional Review Board of our hospital. Due to the retrospective nature of the study (which used data from the cancer data bank of our hospital), informed consent was waived.

From January 2007 through December 2015, 296 patients over the age of 80 who were identified as having histologically confirmed, primary colorectal cancer were evaluated. Among those patients, seventy-four cases were diagnosed as primary rectal cancer and included regardless of tumor stage.

Among those 74 cases, pre-treatment clinical stages II and III were chosen to evaluate treatment outcome. The clinical stage is evaluated by computed tomography scan and physical examination including digital rectal exam. Among those 74 cases, 29 cases were pre-treatment clinical stages II or III including eight cases that were clinical stage II and 21 cases that were clinical stage III. Eighteen of 29 patients were between 80~84 years of age, eight were between 85~90 years old, and three patients were older than 90

years. There were 7 cases with low rectal cancer < 5 cm from anal verge, 19 cases of middle rectal cancer located within 6-10 cm of the anal verge, and 4 cases with upper rectal tumor locating more than 10 cm above dental line.

Patients were further classified into the following three categories: no surgical intervention, only stool diversion with colostomy (including T colostomy or S colostomy), and tumor resection (low anterior resection with/without protective ileostomy, Hartmann's operation, and abdominal perineal resection). Radiation therapy was delivered by a linear accelerator with photon energy. Rectal cancer with clinical T3 at least or regional lymph node metastasis were all received radiotherapy in our study. Between 45~48 Gy with 1.8 Gy per fraction in 5 weeks intervals were delivered under the supervision of several radiation oncologists. All patients were initially prescribed uracil-tegafur (UFUR/UTF) which is an oral prodrug of 5-FU containing 100 mg tegafur and 224 mg uracil. Folinic acid was also prescribed. UFUR/FOLINA was continued for at least 1 year until either treatment failure, occurrence of infection, or worsening general condition. The total daily dose of each drug was divided into two or three equal doses and both drugs were taken together. Oral Xeloda or Folfox were suggested if disease progression or recurrence occurred.

Statistical analysis

General health information on all patients was obtained from hospital records and the government health unit. Survival curves were computed using cox regression analysis. SPSS software, version 15.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analysis.

Results

There were 296 patients who were older than 80-year-old when was diagnosed as colorectal cancer from 2007 to 2015. Among those 296 patients, 29 cases were diagnosed as clinical stage II or III histologically-confirmed rectal cancer. Demographic data from the 29

patients older than 80 years of age is shown in Table 1. Their median age at diagnosis was 84.07 years, with a range of 80 to 82 years. Only four patients had no systemic disease. A total of 16/29 (55%) patients had more than two comorbid illnesses. Hypertension (HTN), diabetes (DM), chronic obstructive pulmonary disease (COPD), cerebral vascular accident (CVA), and dementia were common comorbidities among these patients.

Twelve patients underwent surgery involving tumor resection with or without colostomy or ileostomy. Only one patient received tumor resection secondary to obstruction, involving low anterior resection with protective T loop colostomy. Four patients received T colon or S colon colostomy but no tumor resection was performed. All patients who underwent surgery received emergent surgery due to obstruction caused by tumor. Unfortunately, those patients had no further surgical resection after their bowel obstruction was treated. Only one patient expired from pneumonia during the hospital course for surgery.

Eighteen patients received oral chemotherapy with UFUR/UTF or 5FU injection. Of those patients, 13 patients received adjuvant chemotherapy involving oral UFUR and folina and five patients only received neoadjuvant concurrent chemoradiotherapy. Among the 13 patients who did not undergo surgery, 61% received palliative chemotherapy, and only one patient did not received radiotherapy. For patients who underwent tumor resection, there were eight pa-

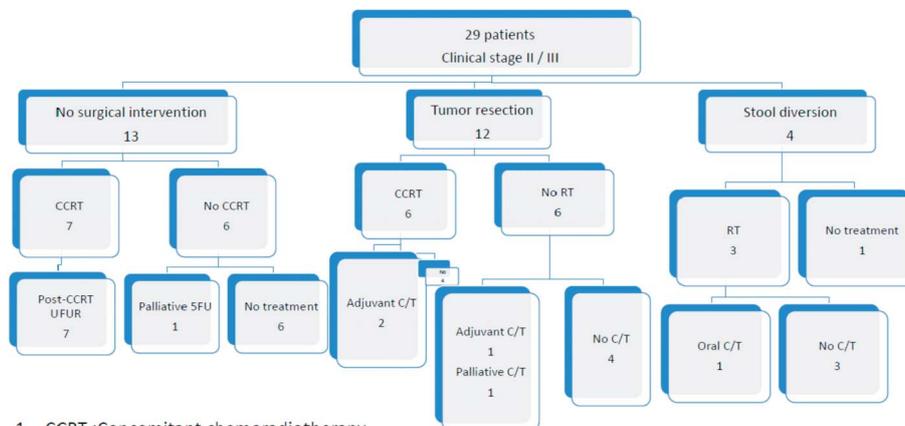
tients who received chemotherapy with UFUR/UTF or Xeloda. Half of the patients received chemotherapy combined with radiotherapy only and no adjuvant chemotherapy was used. Half the patients received adjuvant chemotherapy. Among those patients who received oral chemotherapy, 83% (15/18) of patients received oral UFUR or UTF only. No patients expired due to infection while being treated with chemotherapy.

Radiation therapy was given to 55% (16/29) of patients. Only one patient did not receive a total course of radiotherapy (i.e., received only 70% of the planned dose) and this patient stopped radiotherapy due to fever. All patients received preoperative neoadjuvant radiotherapy with or without chemotherapy, and some patients received palliative radiotherapy. For those patients who received radiotherapy, 25% (4/16) of patients were pathologic stage T2N0M0 after tumor resection.

Outcomes and survival data from all 29 patients were completed in November 2016. Of the 29 patients older than 80 years of age who were diagnosed with rectal cancer from 2007 to 2016, 21 (75%) patients died during follow-up. Of those patients who died, 57.1% (12/21) had deaths recorded as being due to their cancer (Table 2).

Cox multivariate analysis was used to evaluate the rectal cancer patients by age, treatment choice, and gender. There was no survival benefit between tumor resection and no surgery based on the results of the

Table 1.



- 1. CCRT :Concomitant chemoradiotherapy
- 2. RT : Radiotherapy
- 3. C/T : Chemotherapy

multivariate analysis (Fig. 1). There was also no survival benefit for patients receiving radiotherapy (Fig. 2). The only factor affecting survival was choice of chemotherapy (Fig. 3).

Discussion

It is difficult to treat rectal cancer patients over 80 years of age due to the significant risks associated with this particular patient group. According to the literature, age is a major risk for cancer surgery, especially surgery for rectal cancer.⁴ However, improvements in minimally invasive surgery and general care have had no significant effect on either morbidity or hospital stay between elderly and middle-age patients.⁵ With the exception of surgery performed for rectal cancer, neoadjuvant and/or adjuvant therapy had the same overall survival results. For stage II and stage III patients over 80 years of age, neoadjuvant and/or adjuvant therapy plus surgery achieved better survival outcomes.⁶

Table 2. Etiology of death

	Survival	Death	Cancer-related
No surgery	2	11	6
Tumor resection	6	6	3
Bypass	0	4	3

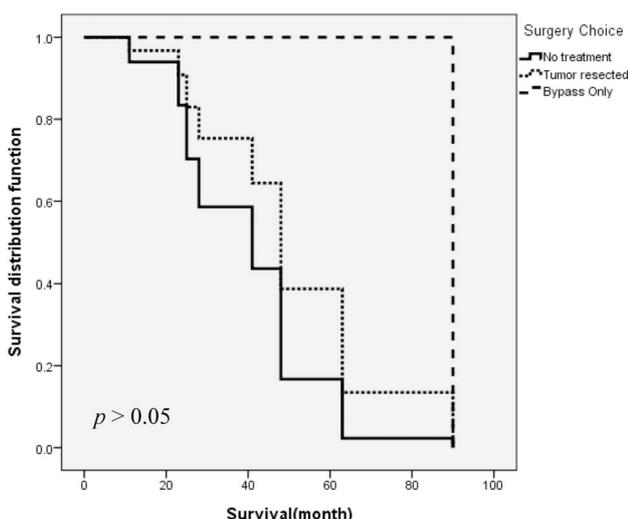


Fig. 1. Cox regression multivariate analysis, surgery choice effect.

Unfortunately, patients older than 80 years often have several comorbidities and low toleration for infections such as pneumonia or urinary tract infections. Those conditions prevent elderly patients from receiving complete postoperative therapy. Based on the Death Statistics of Taiwan of 2013, 12.8% of deaths were due to heart disease and 8.5% of deaths were due to pneumonia in 65-year-old patients.⁷ Thus, when discussing treatment options, clinicians must carefully explain to the family the risks and benefits of rectal

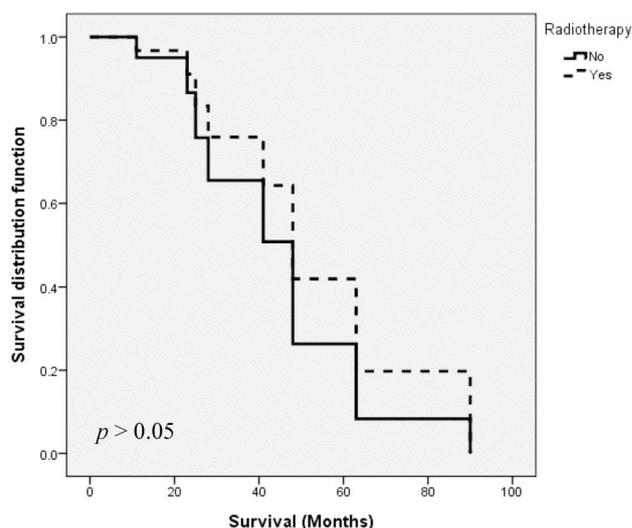


Fig. 2. Cox regression multivariate analysis, radiotherapy choice effect.

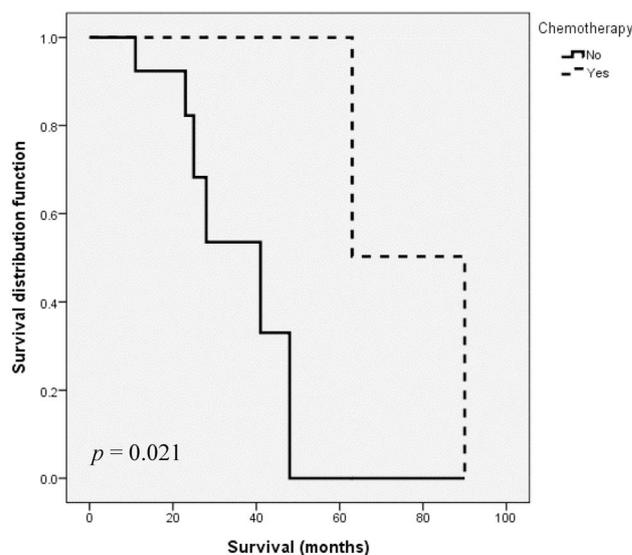


Fig. 3. Cox regression multivariate analysis, chemotherapy choice effect.

cancer treatment including the risk of death by non-cancer etiologies.

Based on several recent studies,^{8,9} definitive surgery is no longer recommended in older patients who are s/p neoadjuvant concurrent chemoradiotherapy with complete response. A “wait-and-see” approach provides an acceptable outcome for these patients. Unfortunately, partial response is still more common in older patients with rectal cancer. Initial assessment of our cases upon treatment showed no survival difference between patients who underwent tumor resection and those without resection. But for patients who received only stool diversion surgery, survival outcomes varied widely (between 1~23 months).

Patients who underwent only bypass surgery had their surgery performed because of obstruction and received emergent surgery. Of those cases, one patient expired due to choking and pneumonia and all others died due to disease progression. Compared with patients without obstruction receiving tumor resection or not without adjuvant chemotherapy, those who underwent tumor resection had better survival (Fig. 4), however, this result needs to be confirmed by larger case studies. This result suggests that tumor resection is still a better option if a patient will not undergo adjuvant chemotherapy and the patient has anal pain,

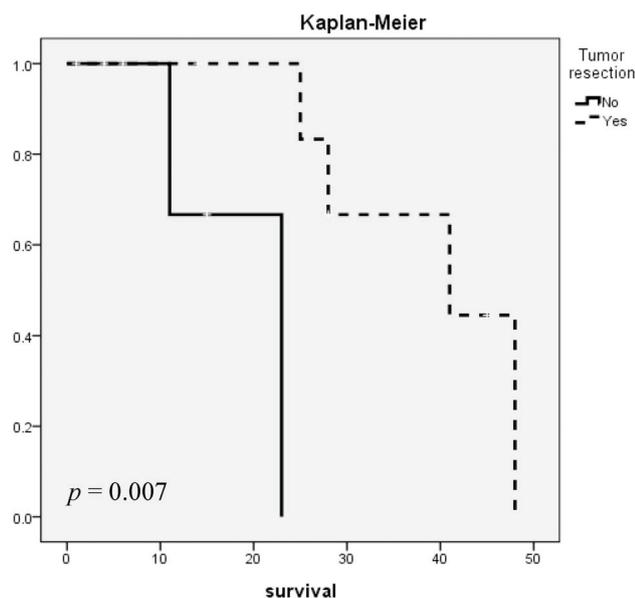


Fig. 4. Kaplan-Meier survival curve for patients without adjuvant chemotherapy.

bleeding, partial or complete obstruction, or tenesmus.

Overall survival of CRC patients is also affected by postoperative chemotherapy.^{10,11} Chemotherapy including oxaliplatin and 5FU is more effective than oral UFUR.¹² However, elderly patients are less tolerant of the prescribed dose which worsens with age. Previous research also showed that patients older than 70 years experienced no obvious difference in benefit between FOLFOX and oral UFUR. For patients older than 80 years, FOLFOX is rarely used in our hospital. Elderly patients in our hospital take only UFUR if they require chemotherapy for their CRC due to their fear of possible side effects and possible reduced quality of life. Of the 21 cases with clinical stage III rectal cancer, only 16 cases received chemotherapy. Of those 16 patients, 13 received oral UFUR, two patients took Xeloda, and one patient received 5FU injection. During their course of therapy, four patients stopped their oral UFUR or xeloda because of infection (i.e., pneumonia, GI infection, perianal abscess, and colitis) and two patients had disease progression. However, based on our multivariate analysis, chemotherapy with only oral UFUR or Xeloda still provided survival benefit.

Unlike chemotherapy, most patients who received radiotherapy received the entire planned course. There were no major complications of radiotherapy and only one patient could not complete radiotherapy. The major benefit of radiotherapy for rectal cancer is improved local control rate.¹³ However, the combination of TME and chemotherapy provided better outcomes. Our results showed radiotherapy has no benefit on overall survival in older patients but radiotherapy still appeared to afford better tumor dissection during surgery. In addition, of the 15 cases who received neoadjuvant concurrent chemoradiotherapy or palliative radiotherapy, there was one patient who had a complete response.

Conclusions

Adjuvant oral chemotherapy appears feasible in patients older than 80 years of age and affords better survival. However, future studies involving larger, older cohorts are needed to confirm our results.

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No.

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原 著

高齡臨床分期第 2、3 期直腸癌治療選項 相關預後的分析

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目的 大腸直腸癌的發病率隨著年齡的增長而增加,其中針對直腸癌的治療包括手術切除、化學療法和放射治療。然而,老年是所有治療的重要風險而且具有較高的合併症和死亡率。此外,老年患者除了癌症之外,還會遇到其他內外科嚴重疾病及導致的死亡。在本文中,我們收集 80 歲以上患者的資料,並分析相關治療選擇的生存獲益及死亡統計。

方法 回顧分析了本院 2007 年至 2015 年診斷為臨床分期第 2 或 3 期直腸癌的台北慈濟醫院病人的病歷資料,對患者的臨床特徵、治療選擇、預後及死亡病因進行比較分析。

結果 診斷為臨床分期第 2 或 3 期組織學確診直腸癌 29 例,29 例患者中有 18 例在 80~84 歲之,8 例在 85~90 歲之間,3 例患者 90 歲以上。55% 的患者擁有兩種以上的重大內科疾病,75% 的患者追蹤期間死亡,在死亡的患者中,有 57.1% 的患者死於癌症相關因素。經多變量 cox 回歸分析,只有術後輔助化療具有統計學生存益處。

結論 在高齡直腸癌患者的治療方式上,有接受輔助化學治療(口服 5FU)有較好的預後且沒有重大併發症。

關鍵詞 高齡直腸癌、治療選項、預後。