International Journal of Management, Economics and Social Sciences
Special Issue-International Conference on Medical and Health Informatics (ICMHI 2017)
2018, Vol. 7(S1), pp.142 – 154.
ISSN 2304 – 1366
http://www.ijmess.com

Benefits of Pre-Operative Concurrent Chemo-Radiotherapy among Elder Patients with Local Advanced Rectal Cancer

[*]Wen-Chien Ting[1]
Chih-Jung Yeh[2]

[1]Dept. of Colorectal Surgery, Chung Shan Medical University Hospital, Taichung, Taiwan
[2] Dept. of Public Health, Chung Shan Medical University, Taichung, Taiwan

The pre-operative chemo-radiotherapy (Pre-OP CCRT) in aged patients with stage III rectal cancer may be less effective. We collected data from 3365 patients (2004-2012) from Taiwan Cancer Registry. Metachronous colorectal cancer and multiple cancer patients were excluded. The patients were separated in three groups, operation first, Pre-OP CCRT first and treatment without operation. SAS 9.2 Student-t, ANOVA and Chi-Square tests were used for analysis. It was found that Group II had good survival curve than the group I (HR =0.26, p<0.0001). The group III had the worst survival benefit (HR=3.38, p<0.0001). Patients with age <75 Y/O had the same survival curve (p=0.0099). Patients age between75-80Y/O had worse survival time (HR=2.91, p<0.0001). The mortality rate increased dramatically in patients old than 85Y/O but the Pre-OP CCRT still provided survival benefit (HR=6.55, p<0.0001). Pre-operative CCRT improved survival in stage III rectal cancer. Even patients with 80~85 years old still had the benefit. In old patients without major comobility and good physical status, Pre-OP CCRT was still the best choice.

Keywords: Pre-operative concurrent chemo-radiotherapy (Pre-op CCRT), rectal cancer, local recurrence, survival time

The incidence of colorectal cancer (CRC) has increased in many countries in recent years. Due to the popularity of lower fiber and high-fat diet, the incidences of CRC elevated gradually. Colorectal cancer become a major cause of morbidity and mortality throughout the world and makes the treatment more important. CRC treatment is mainly done on tumor stage when it is diagnosed. The treatment guidelines for CRC, made by the National Comprehensive Cancer Network (NCCN) in the U.S., is used worldwide. Several countries use it as a standard. But in Taiwan, each hospital owns its modified guidelines according to operational ability rule.

Radical resection of colon cancer is simple in stages I-III, as radiotherapy or neoadjuvant chemotherapy is not necessary due to the movable anatomic structure of the colon. Rectal cancer treatment, however, is

Manuscript received May 23, 2017; revised June 15, 2017; accepted July 20, 2017.
*Corresponding author: tingwenchien@gmail.com

More difficult. Mendenhall *et al*. (1983) found a local advanced tumor (T3 or T4) cannot be controlled easily during operation and a high incidence of local recurrence was observed in the past.

Cedermark *et al*. (1997) presented preoperative concurrent chemoradiotherapy (Pre-OP CCRT) was then used and subsequently became a guideline for the past two decades. The procedure can achieve tumor shrinkage, increase success of the sphincter-saving operation, reduce local recurrences according to Habr-Gama *et al*. (1998), and increase disease-free survival by Jung *et al*. (2015), as well as decrease 5-year overall mortality, cancer-related mortality, and local recurrence rates by Camma *et al*. (2000).

Although the Pre-OP CCRT following with surgery becomes a general rule in rectal cancer treatment, colorectal surgeons in Taiwan may not follow it due to age, patient condition, and/or health insurance payment principle. In clinical practice, not all doctors obey the guideline, particularly when patients are over 75 years old. The factors included ECOG performance status of patients, comorbidity, age beyond life expectancy, and economic support of family.

There are no reports on whether elderly patients benefit by Pre-OP CCRT. Sanoff *et al*. (2012) found patients above 75 years old were excluded from most studies. So the group of old age patients need more attention in clinical practice. Most developed countries set the age of 65 as the beginning of old age. The definitions of old age continue to change as life expectancy in developed countries has risen to beyond 80 years old.

Therefore, it is unclear whether elderly patients receive standard treatment of rectal cancer and if doctors adhere to NCCN treatment guidelines for rectal cancer. In order to address these questions and monitor the treatment of local advanced rectal cancer, we used the database from Taiwan Cancer Registry. Our main objective was to determine whether old patients have the same benefit from Pre-OP CCRT as young patients. The result of this analysis can help doctors make good suggestions to old patients.

LITERATURE REVIEW

CRC is the most prevalent malignancy in Taiwan. Glimelius *et al*. (1995) had reported the incidence of rectal cancer is 35%-45% among all CRCs worldwide. The local failure rate plays an important role in the treatment

of rectal cancer. Scott *et al*. (1995) showed there were many techniques to improve the local failure rate including total mesorectal excision (TME), such as preoperative radiotherapy, CCRT, postoperative adjuvant chemotherapy, postoperative adjuvant CCRT, radiotherapy, etc.

Though many procedures are used, preoperative radiotherapy has been extensively investigated. Early in 1997, study by Cedermark *et al*. (1997) reported an overall 5-year survival rate of 58% in patients who underwent radiotherapy plus surgery and 48% in patients who underwent surgery alone. This is significant improvement of survival improvement in the war to rectal cancer. Since then, information from a number of controlled trials (Habr-Gama *et al*. 1998; Glimelius *et al*., 1995) indicates that the proportion of local recurrences is reduced to less than half when radiotherapy at moderately high doses is given preoperatively. A meta-analysis by Camma *et al*. (2000) showed in patients with resectable rectal cancer, preoperative radiotherapy significantly improved overall and cancer-specific survival compared with surgery alone. The magnitude of the benefit is relatively large and criteria are needed to identify patients most likely to benefit from adjuvant radiotherapy.

According to the NCCN guideline and related papers (e.g., Sebag-Montefiore *et al*. 2009, 2001, Tepper *et al*., 2002, Pucciarelli *et al*., 2000), Pre-OP CCRT is the standard of locally advanced rectal cancer treatment since 2003. Wagman *et al*. (1998) said that sphincter preservation could be achieved in 77% of patients who would otherwise require an abdominoperineal resection. Kachnic (2006) also concluded that preoperative chemoradiation therapy also allowed for the investigation of innovative agents (capecitabine, oxaliplatin, irinotecan, bevacizumab, and cetuximab) in combination with pelvic radiation. In Taiwan, the treatment guideline of all medical centers mainly follows the NCCN guideline, so all patients with rectal cancer are expected to receive the same treatment protocol.

Little data about the benefit of Pre-OP CCRT in elderly patients with rectal cancer. Sanoff and Goldberg (2007) reported the colorectal cancer treatment in older patients but limited the age of patients to 70 years old. A review of National Cancer Institute (NCI)-sponsored trials (Murthy *et al*., 2004) showed only “ 0.3%-0.5% of enrolled patients in these trials were older than 75. Old patients should be an important group in the colorectal cancer patients.

Gerontologists have recognized the diversity of old age by defining sub-groups. Zizza *et al.*(2009) used the sub-grouping as young-old (65 to 74), middle-old (75– 84), and oldest-old (85+). Forman *et al.* (1992) distinguishes the young old (60 to 69), the middle old (70 to 79), and the very old (80+). As there is no literature on the value of the NCCN guideline in elderly patients, we sought to design a study to determine this.

METHODOLOGY

This study used cancer registration data, provided by the Taiwan Cancer Registry, from rectal cancer patients diagnosed with clinical or pathological stage III cancer with no distal metastasis from 2004 to 2012. Patients selected were 18 years of age and above, and were placed into three groups: (1) Patients who underwent direct surgery and had postoperative pathological stage (pStage) III, (2) Patients with clinical stage (cStage) III who underwent tumor resection after Pre-OP CCRT, and (3) Patients with cStage III who underwent chemotherapy, radiotherapy, CCRT, or supportive treatment but did not undergo any tumor resection surgery. Subgroups were made according to the post treatment pathologic stage (ypStage) and following treatments after tumor resection.

In Taiwan, the physical status of people younger than 75 years old seem to be gathered in the same sub-grouping, So each sub-group was further divided into four age groups, namely, 70 years old and below, 70-74 years old, 75-80 years old and 80 years old and above. We analyzed the choice of treatment regimen in each age group and whether there were significant differences in the compliance rates.

What condition means treatment adhere to the guidelines? Certain restrictions were needed for the time course in the experiment, and patients that were unable to complete the treatment regimen within a fixed time period were excluded from this study. For Group 1, the time of diagnosis to day of surgery must be within 60 days, and the start date of postoperative radiotherapy and chemotherapy must be within 90 days from the day of surgery. For Group 2, the time of diagnosis to start date of radiotherapy must be within 60 days and surgery must be carried out within 60 days from completion of radiotherapy. The start date of postoperative chemotherapy must be within 90 days from the day of surgery. For Group 3, patients only

underwent radiotherapy, chemotherapy, CCRT, or were not given treatment at all. Patients also did not undergo tumor resection surgery after diagnosis.

Data processing and statistical analysis was conducted using SAS 9.2 statistical software. Descriptive and correlation statistics analyses were used in the study. Independent and dependent variables were evaluated to find the demographic characteristics of rectal cancer patients (age, gender), treatment course characteristics, and post-treatment status. Survival status and relevant prognosis of rectal cancer patients were also calculated in different treatment regimens (such as with or without radiotherapy), or different age groups after undergoing radiotherapy. The Cox Proportional Hazard Model was used to estimate Hazard Ratios (HR) and 95% confidence intervals.

RESULTS

From 2004 to 2012, the total number of patients in the Taiwan Cancer Registry that fulfilled the inclusion criteria of this study were 3,365. There were 2,040 males and 1,325 females. The average age was 57.1 years. There were 2,004 patients in Group 1, 1,044 patients in Group 2, and 317 patients in Group 3. According to the regulations by the Taiwan Ministry of Health and Welfare, data from groups with fewer than five people were not shown. Therefore, some fields are empty in Table I (see Appendix-I).

Patient demographics and characteristics are listed in Table 1. In Group 1, the most common postoperative adjuvant treatment was CCRT (1,444 patients; 72%), with follow-up as the second treatment plan used (359 patients; 17.9%), and radiotherapy as the least often (19 patients; 0.9%).

The postoperative cancer stage in Group 2 ranged from ypStage 0 to ypStage III. The same preoperative and postoperative stage was observed in 438 patients (42.0%) and the rest had tumor downstaging. The median follow-up times were similar (10.5-12.6 months) among all groups and subgroups except Group 3 (6.6 months) and the F/U subgroup in Group 1 (7.8 months).

The results of the univariate and multivariate Cox regression analyses for cancer-related mortality are listed in Table 2. Univariate analysis using Cox proportional hazard modeling showed the Group 2 had a significant better effect in treatment group (HR 0.26, $^{**}p<0.001$). The Group 3 patients had high cancer-related mortality than the patients in Group 1 (HR 3.38, $^{**}p<0.001$). The survival curve is shown in Figure 1. In Age group (Figure 2), the patients aged 70-75 seemed to have trend about worse survival benefit than the

patients aged below age 70 , but there is no statistical difference in multivariate Cox regression model (HR 1.03, p=0.04). And the patients age 75-80 and age >= 80 had high mortality rate than patient aged below 70. The same results were also noted in multivariate Cox regression model. The Group 2 showed best survival benefit despite patient in all age group (Figure 2, 3)

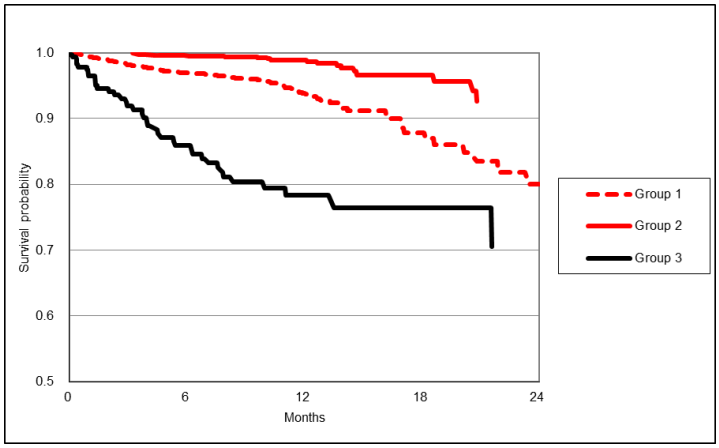

Figure 1. Survival Probability by Treatment Group

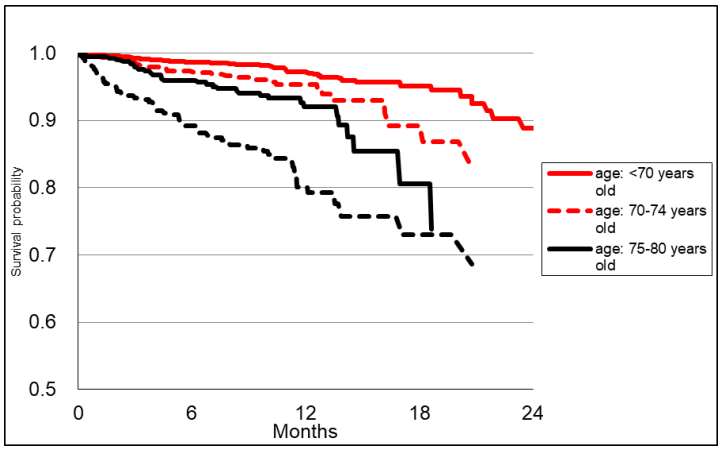

Figure 2. Survival Probability by Age Group

DISCUSSION

Preoperative CCRT has been included in the rectal cancer treatment guidelines of the world and Taiwan for more than 10 years. Hines *et al.* (2015) has reported the guideline-adherent treatment was received by

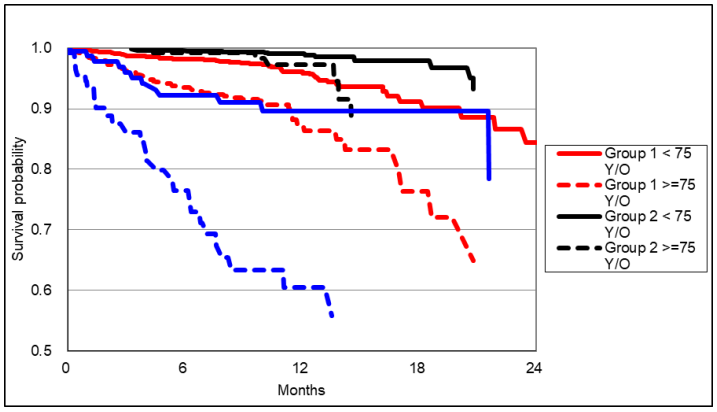

Figure 3. Survival Probability by 75 Y/O Boundary

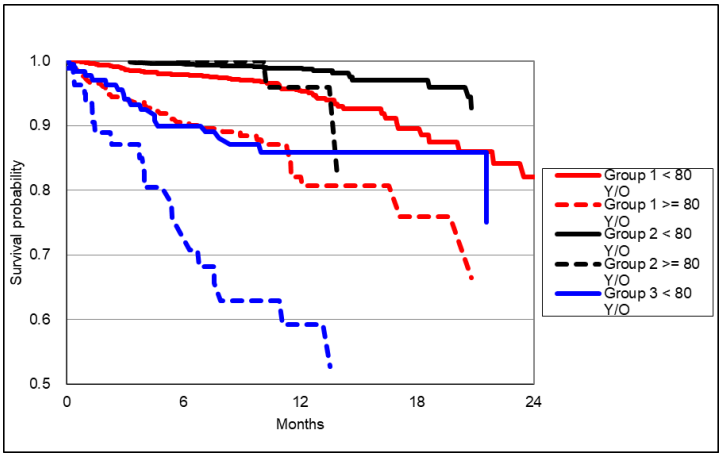

Figure 4. Survival Probability by 80 Y/O Boundary

	Univariate Cox regression			Multivariate Cox regression		
	HR	95% C.I. of HR	P value	HR	95% C.I. of HR	P value
Treatment group						
Group 2 vs. Group 1	0.26	[0.16,0.42]	<0.001	0.32	[0.20,0.52]	<0.0001
Group 3 vs. Group 1	3.38	[2.36,4.85]	<0.001	2.70	[1.67,3.90]	<0.0001
Age group						
Aged 70-75 vs. aged <70	1.83	[1.16,2.90]	0.0099	1.03	[1.03,2.59]	0.0375
Aged 75-80 vs. aged <70	2.91	[1.90,4.46]	<0.001	2.66	[1.73,4.07]	<0.0001
Aged >=80 vs. aged <70	6.55	[4.61,9.30]	<0.001	4.44	[3.09,6.36]	<0.0001

Table 2. Univariate and Multivariate Cox Regression for Cancer Related Mortality (N=3365)

82.7% of patients. However, according to the data collected in this study, there were more patients that did not receive Pre-OP CCRT (groups 1 and 3; 69%) compared to those that did receive Pre-OP CCRT (Group

2; 31%), suggesting that the percentage of adherence in Taiwan is lower. Thus, there is a gap in current awareness that most physicians obey the treatment guideline as far as possible. Because there appears to be a discrepancy between real-world practice and treatment guidelines in the treatment of rectal cancer, the reasons behind this discrepancy should be investigated. Patients may refuse the suggestion in treatment plan due to lack of medical knowledge and poor physical status (ECOG). In Taiwan, the family support system plays a major role in the treatment selection of patients.

With regard to Group 1, a majority of patients (72.1%) underwent postoperative adjuvant CCRT. This was followed by adjuvant chemotherapy (CT) (9.1%). The number of patients who underwent adjuvant radiotherapy (RT) was very low (0.9%). However, about 17.9% of patients did not undergo any CT or RT following surgery. This group of patients was relatively older in age (average 70.3 years) compared to patients who received postoperative treatment, whereas the average age of patients who underwent adjuvant CCRT was the lowest (add average). Thus, the physician may adjust the postoperative adjuvant treatment based on age.

The number of patients in Group 2 was lower than expected. As mentioned previously, this group of patients accounted for 31% of the total patients in this study, and the subgroup distribution was extremely uneven, with some subgroups housing less than ten patients. The reason for this could be that the preoperative clinical stage of all rectal cancer patients was determined using computed tomography imaging. However, a pelvic computed tomography scan could detect regional lymph node enlargement, and few patients fulfilled the criteria for stage III. This is due to the limitations in imaging precision and AJCC guideline (Edge *et al.*, 2010) also states that lower stages cannot be determined as the clinical stage of patients. The number of patients may not match the physician's expectation by stage, thus the number patients with clinical stage III cancer may be underestimated. To improve classifying clinical stage, magnetic resonance imaging (MRI) was advised by some physicians (Adeyemo and Hutchinson, 2009, Nerad *et al.*, 2017). Positron Emission Tomography (PET)-CT is also a more useful and powerful tool to accurately determine staging of tumors compared to traditional CT (Buijsen *et al.*, 2011).

The number of patients in Group 2 who underwent Pre-OP CCRT, did not have any tumor cells in postoperative specimens, and achieved complete tumor remission (ypStage 0) was very low (7 patients; <1%). This is lower than the 17%– 25% reported in the literature (Maas *et al.*, 2010, Yoon *et al.*, 2015). The difference may be due to the reason that this study used a Taiwanese population or the earlier inclusion date of patients in the Taiwan Cancer Registry. A report by Lee *et al.* (2008) also had a low complete response rate (5.3%) in Korea, but this is still higher than what we report. More data is needed to determine the reason for this difference.

There were 599 patients (57%) in Group 2 that were downstaged to ypStage I and ypStage II. Yang *et al.* (2005) reported the TNM stage after Pre-OP CCRT, where 60% of patients were downstaged, and similarly, Lee *et al.* (2008) reported a downstaging rate of 52.6%. Our results are consistent with these previous reports, suggesting that about half of rectal cancer patients may have an advantage in receiving the procedure.

The majority of patients in groups 1 and 2 were aged 70 and below. There were no large differences in the number of patients aged 70-75, 75-80, and older than 80 years. However, in Group 3, the number of patients with 80 years of age or older were the largest among the three treatment groups (n = 87; 27.5%) while the number of patients 70 years old and younger were the lowest (n = 128; 49.8%), which was lower than half the number of patients. A similar trend for adjuvant treatment can be found in Group 1. The average age (70.3 years) in the follow-up (F/U) group is older than the other three subgroups (Table 1). Age appeared to be a major factor when selecting treatment regimen. According to the Cox regression analysis and the survival curves, significant differences in cancer-related mortality were seen when the data was split by age, with patients 80 years and older showing greater mortality rates and patients 75 years and older showed lower patterns of survival compared to their younger counterparts. Zizza *et al.* (2009) and Forman *et al.* (1992) had reported the different sub-groupings for "old", we can distinguishes the young old (65 to 74), the middle old (75 to 79), and the very old (80+) in Taiwan CRC patients. In our study, for patients aged 80 years and older, survival rates could decrease drastically (Figure 4). However, if patients aged 75 years and older underwent appropriate surgery, their survival rates could approach that of patients aged below 75 who did not undergo surgery (Figure 3).

Group 2 had the best treatment outcome, with Group 1 showing better prognosis compared to Group 3. There were no significant differences for patients under 75 years of age. Differences start to appear in the age group of 75-80 years, and mortality probability starts to drastically increase at age 85 years and older. Preliminary results from a follow-up period of 24 months showed that the Pre-OP CCRT group had the best survival rate regardless of age. This result may be useful for modifying current treatment guidelines (Jung *et al.*, 2015).

CONCLUSION

Factors associated with guideline adherence included age, comorbidity index, insurance status, and level of hospital. Pre-OP CCRT is currently used as a standard treatment for stage III rectal cancer. It was not known if elderly patients benefited from the procedure; now, the results of this study suggest that these patients (even patients older than 80 years old) can still follow the guideline. Pre-OP CCRT following with operation results is the best outcome of this study and the literature review. The guideline is suitable in Taiwan also. Physicians could suggest patients receive the treatment procedure regardless of the age.

LIMITATIONS AND FUTURE DIRECTIONS

This study did not use the death registry; therefore, we were unable to accurately obtain the time of death. In addition, the cancer registry staff registered patients' data within one year of diagnosis and uploaded data according to year, so 3-year and 5-year survival data are not available. We are awaiting access to health insurance data to tabulate the Charlson Comorbidity Index and treatment choice according to existing subgroups, in order to determine the actual survival rate and disease progression rate.

Some stage III patients did not undergo resection surgery, and the reasons for this could not be obtained using the cancer registry. It is possible that these patients may have comorbidities and were unable to undergo surgery, that they have high surgery risk, or that the patient and their family members refuse radical surgery. We found that patients in Group 3 had very low survival rates and almost all patients died within two years. To determine whether comorbidity factors influenced our results, further access to health insurance data is needed.

REFERENCES

Adeyemo, D. & R. Hutchinson (2009). Preoperative staging of rectal cancer: pelvic MRI plus abdomen and pelvic CT. Does extrahepatic abdomen imaging matter? A case for routine thoracic CT. *Colorectal Disease,* 11**,** 259-63.

Buijsen, J., J. van den Bogaard, M. H. Janssen, F. C. Bakers, S. Engelsman, M. Ollers, R. G. Beets-Tan, M. Nap, G. L. Beets, P. Lambin & G. Lammering (2011). FDG-PET provides the best correlation with the tumor specimen compared to MRI and CT in rectal cancer. *Radiotherapy and oncology,* 98**,** 270-6.

Camma, C., M. Giunta, F. Fiorica, L. Pagliaro, A. Craxi & M. Cottone (2000). Preoperative radiotherapy for resectable rectal cancer: A meta-analysis. *Journal of the American Medical Association,* 284**,** 1008-15.

Cedermark, B., M. Dahlberg, B. Glimelius, L. Pahlman, L. E. Rutqvist & N. Wilking (1997). Improved survival with preoperative radiotherapy in resectable rectal cancer. *The New England Journal of Medicine,* 336**,** 980-7.

Colorectal Cancer Collaborative Group. (2001). Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. *The Lancet,* 358**,** 1291-304.

Edge, S.B., Byrd, D.R., Compton, C.C., Fritz, A.G., Greene, F.L. & Trotti, A. (2010). Eds. AJCC Cancer Staging Manual. 7th ed. New York: Springer.

Forman, D. E., A. D. Berman, C. H. McCabe, D. S. Baim & J. Y. Wei (1992). PTCA in the elderly: the "young-old" versus the "old-old". *Journal of the American Geriatrics Society,* 40**,** 19-22.

Glimelius, B., U. Isacsson, B. Jung & L. Pahlman (1995). Radiotherapy in addition to radical surgery in rectal cancer. *Acta Oncologica,* 34**,** 565-70.

Habr-Gama, A., P. M. de Souza, U. Ribeiro, Jr., W. Nadalin, R. Gansl, A. H. Sousa, Jr., F. G. Campos & J. Gama-Rodrigues (1998). Low rectal cancer: impact of radiation and chemotherapy on surgical treatment. *Diseases of the Colon & Rectum,* 41**,** 1087-96.

Hines, R. B., A. Barrett, P. Twumasi-Ankrah, D. Broccoli, K. K. Engelman, J. Baranda, E. A. Ablah, L. Jacobson, M. Redmond, W. Tu & T. C. Collins (2015). Predictors of guideline treatment nonadherence and the impact on survival in patients with colorectal cancer. *Journal of the National Comprehensive Cancer Network,* 13**,** 51-60.

Jung, K. U., H. C. Kim, J. O. Park, Y. S. Park, H. C. Park, D. H. Choi, Y. B. Cho, S. H. Yun, W. Y. Lee & H. K. Chun (2015). Adjuvant chemotherapy after neoadjuvant chemoradiation and curative resection for rectal cancer: is it necessary for all patients? *Journal of Surgical Oncology,* 111**,** 439-44.

Kachnic, L. A. (2006). Should preoperative or postoperative therapy be administered in the management of rectal cancer? *Seminars in Oncology,* 33**,** S64-9.

Lee, S. H., K. C. Lee, J. H. Choi, J. H. Oh, J. H. Baek, S. H. Park & D. B. Shin (2008). Chemoradiotherapy followed by surgery in rectal cancer: improved local control using a moderately high pelvic radiation dose. *Japanese Journal of Clinical Oncology,* 38**,** 112-21.

Maas, M., P. J. Nelemans, V. Valentini, P. Das, C. Rodel, L. J. Kuo, F. A. Calvo, J. Garcia-Aguilar, R. Glynne-Jones, K. Haustermans, M. Mohiuddin, S. Pucciarelli, W. Small, Jr., J. Suarez, G. Theodoropoulos, S. Biondo, R. G. Beets-Tan & G. L. Beets (2010). Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. *The Lancet Oncology,* 11**,** 835-44.

Mendenhall, W. M., R. R. Million & W. W. Pfaff (1983). Patterns of recurrence in adenocarcinoma of the rectum and rectosigmoid treated with surgery alone: implications in treatment planning with adjuvant radiation therapy. *International Journal of Radiation Oncology • Biology • Physics,* 9**,** 977-85.

Murthy, V. H., H. M. Krumholz & C. P. Gross (2004). Participation in cancer clinical trials: race-, sex-, and age-based disparities. *Journal of the American Medical Association,* 291**,** 2720-6.

Nerad, E., D. M. Lambregts, E. L. Kersten, M. Maas, F. C. Bakers, H. C. van den Bosch, H. I. Grabsch, R. G. Beets-Tan & M. J. Lahaye (2017). MRI for Local Staging of Colon Cancer: Can MRI Become the Optimal Staging Modality for Patients With Colon Cancer? *Diseases of the Colon & Rectum,* 60**,** 385-392.

Pucciarelli, S., M. L. Friso, P. Toppan, A. Fornasiero, S. Carnio, E. Marchiori & M. Lise (2000). Preoperative combined radiotherapy and chemotherapy for middle and lower rectal cancer: preliminary results. *Annals of Surgical Oncology,* 7**,** 38-44.

Sanoff, H. K., W. R. Carpenter, T. Sturmer, R. M. Goldberg, C. F. Martin, J. P. Fine, N. J. McCleary, J. A. Meyerhardt, J. Niland, K. L. Kahn, M. J. Schymura & D. Schrag (2012). Effect of adjuvant chemotherapy on survival of patients with stage III colon cancer diagnosed after age 75 years. *Journal of Clinical Oncology,* 30**,** 2624-34.

Sanoff, H. K. & R. M. Goldberg (2007). Colorectal cancer treatment in older patients. *Gastrointestinal Cancer Research,* 1**,** 248-53.

Scott, N., P. Jackson, T. al-Jaberi, M. F. Dixon, P. Quirke & P. J. Finan (1995). Total mesorectal excision and local recurrence: a study of tumour spread in the mesorectum distal to rectal cancer. *British Journal of Surgery,* 82**,** 1031-3.

Sebag-Montefiore, D., R. J. Stephens, R. Steele, J. Monson, R. Grieve, S. Khanna, P. Quirke, J. Couture, C. de Metz, A. S. Myint, E. Bessell, G. Griffiths, L. C. Thompson & M. Parmar (2009). Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *The Lancet,* 373**,** 811-20.

Tepper, J. E., M. O'Connell, D. Niedzwiecki, D. R. Hollis, A. B. Benson, 3rd, B. Cummings, L. L. Gunderson, J. S. Macdonald, J. A. Martenson & R. J. Mayer (2002). Adjuvant therapy in rectal cancer: analysis of stage, sex, and local control--final report of intergroup 0114. *Journal of Clinical Oncology,* 20**,** 1744-50.

Wagman, R., B. D. Minsky, A. M. Cohen, J. G. Guillem & P. P. Paty (1998). Sphincter preservation in rectal cancer with preoperative radiation therapy and coloanal anastomosis: long term follow-up. *International Journal of Radiation Oncology • Biology • Physics,* 42**,** 51-7.

Yang, S. H., R. C. Lee, C. C. Chen, J. K. Jiang, J. K. Lin, A. F. Li, W. Y. Liang & L. W. Wang (2005). Is decrease of tumor volume correlated with stage change after preoperative concurrent chemoradiotherapy? *Hepatogastroenterology,* 52**,** 765-9.

Yoon, W. H., H. J. Kim, C. H. Kim, J. K. Joo, Y. J. Kim & H. R. Kim (2015). Oncologic impact of pathologic response on clinical outcome after preoperative chemoradiotherapy in locally advanced rectal cancer. *Annals of Surgical Treatment and Research,* 88**,** 15-20.

Zizza, C. A., K. J. Ellison & C. M. Wernette (2009). Total water intakes of community-living middle-old and oldest-old adults. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences,* 64**,** 481-6.

ACKNOWLEDGEMENT

This research is sponsored by the Chung Shan Medical University Hospital, under Grant no CSH-2013-A-040.

Appendix-I

Treatment		Group I				Group II								Group III
Tatal Number (%)		2004 (59.56%)				1044 (31%)								317 (9.4%)
Stage		pStage III				ypStage 0		ypStage I		ypStage II		ypStage III		cStage III
		F/U	CCRT	RT	CT	F/U	CT	F/U	CT	F/U	CT	F/U	CT	--
Number (% in each group)		359 (17.9%)	1444 (72%)	19 (0.9%)	182 (9.1%)	5 (0.48%)	2 (0.2%)	117 (11.2%)	129 (12.4%)	149 (14.3%)	204 (19.5%)	119 (11.4%)	319 (30.6%)	317
Median F/U time (Month)		7.8	11.6	11.0	12.6	10.5	--	15.7	12.4	14.3	12.7	14.3	12.4	6.6
Time from CCRT to surgery (Day)		--	--	--	--	45.8	--	43.7	48.8	43.9	45.0	45.0	43.2	--
No.	<70 Y/O	1196 (69.7%)				785 (75.2%)								128 (49.8%)
	70-75 Y/O	279 (13.9%)				127 (12.2%)								37 (11.7%)
	75-80 Y/O	268 (13.4%)				94 (9.0%)								35 (11.0%)
	>=80 Y/O	261 (13.0%)				38 (3.6%)								87 (27.5%)
Age Average		70.3	64.3	67.3	63.3	51.7	--	62.2	60.2	60.8	59.9	60.0	59.1	68.8
Gender	M	1154 (57.6%)				692 (66.3%)								194 (61.2%)
	F	850 (42.4%)				352 (33.7%)								12 (38.8%)

F/U: follow-up, CCRT: concurrent chemohradiotherapy, RT: radiotherapy, CT: chemohterapy
Group II: all were cStage II

Table 1. Demographic Characteristics of All Patients (N=3365)