

Neoadjuvant Chemoradiotherapy for Advanced Rectal Cancer

Abdolhassan Talaiezadeh^{*1}, Hodjatollah Shahbazian², Mohammad Hosein Sarmast Shushtari³, Seyyed Mohammad Hoseini², Seyyed Saheb Hoseininejad⁴

¹Professor of general surgery and surgical oncology, Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran & Petroleum & Environmental Pollutant Cancer Research Center.

²Assistant Professor of radiotherapy and oncology, Department of Radiotherapy and Oncology, Golestan Hospital, Ahvaz Jundishapur University of Medical Science, Ahvaz, Iran

³Professor of general surgery, Department of Surgery, Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical Science, Ahvaz, Iran

⁴General Surgeon, Department of Surgery, Razi Hospital, Ahvaz Jundishapur University of Medical Science, Ahvaz, Iran.

*Corresponding author: Abdolhassan Talaiezadeh, Petroleum & Environmental Pollutant Cancer Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. E-mail: ah.talaiezadeh@ajums.ac.ir

Received: Jan 18, 2016; Revised: Mar 5, 2016; Accepted: Apr 6, 2016

Abstract

Background: There is some evidence that neoadjuvant chemoradiation for stages II and III rectal tumors associated with significant greater rate of complete pathologic response and sphincter preservation. The aim of this study was to determine the outcome of neoadjuvant chemoradiation in patients with advanced rectal cancer.

Materials and Methods: In this retrospective investigation, the medical records of all patients with stage II or III that underwent neoadjuvant chemoradiation (during 2005-2010) were studied. Radiotherapy was delivered by 4500-5000cGy/25-28f for 25-28 sessions, and oral 5-FU and weekly injected Eloxatin were administered. Then, all patients underwent surgery by one expert oncologist surgeon. Data include demographic data, the kind of operation, the rate of pathologic complete response and clear surgical margins and sphincter preservation were collected. Data were analyzed with SPSS software version 14.

Results: Among 70 patients, the mean age was 46±13 years and 71.5% of them were male. Ten percent had the pathologic complete response, 60% had clear surgical margins. Sphincter preservation rate in cases which the distance of the tumor from anal verge was five cm or more and in cases which it was less than five cm were 51.4% and 5.6%, respectively.

Conclusion: Our results indicated that neoadjuvant chemoradiation recommended for patients with the stages II and III rectal cancers. The advantages of this modality are relatively higher chance of complete response and anal sphincter saving procedure.

Keywords: Neoadjuvant chemoradiation, rectal cancer, sphincter saving procedure, TME.

Background

Colorectal cancers are currently one of the most important health issues around the world. This cancer is the third most common cancer and the fourth leading cause of death from the cancer in the world. Its incidence is 40.1 per 100,000 per year in the United States. And its mortality rate is 14.8 per 100,000 annually (1, 2). Studies in Iran also indicate that the colorectal cancer incidence is 7–8 per 100,000 (3). Considering the high prevalence of rectal cancer as a life-threatening disease, which has high death, morbidity and disability, using a modern therapeutic method for the cure of these patients is necessary (2-8).

There are different therapeutic methods for this disease like surgery, radiation, and chemotherapy (4). From the past, for the advanced cases stages >II, the method had been first surgery and excision of the tumor together with rectum and local lymph nodes (2,4-7). Since two decades ago, the National Institutes of Health Consensus recommended neoadjuvant chemoradiation and subsequently total mesorectal excision (TME) as the standard treatment for locally advanced rectal cancers (8). In this modality the patient first, gets chemoradiation regimen therapy and after shrinkage of the tumor, the patient undergoes surgery whether as abdominoperineal resection (APR) or sphincter preserving procedure according to distance of tumor

from anal verge as low anterior resection (LAR) or extended low anterior resection (ext. LAR) (2,4-7).

Some evidence suggests that treatment with preoperative neoadjuvant chemoradiation with or without chemotherapy method, combined with TME, reduces the incidence of local recurrence, marginally positive and improvement of complete pathological response, as well as increased chance of sphincter preserving procedure and improved survival and quality of life. Also, in some studies preoperative chemoradiation treatment was concomitant with reduced the rate of relapse and decrease the tumor stage (4-8).

Unfortunately, there was no study determined the effect of neoadjuvant chemoradiation on the outcomes of locally advanced rectal cancer patients in southwest of Iran. So, we designed this study to evaluate the outcomes of neoadjuvant chemoradiation method on the patients with rectal cancer in the academic centers of Ahvaz Jundishapur University of Medical Sciences during 2005- 2010.

Materials and Methods

In this retrospective investigation, the medical records of all patients with stage II or III that underwent neoadjuvant chemoradiation (during 2005-2010) in

Radiotherapy and Oncology Ward of Golestan Hospital as the referral center of chemoradiotherapy (CRT) in southwest of Iran were studied. The necessary data include demographic data were registered in a checklist. The patients first received neoadjuvant chemoradiation with daily capecitabine 825mg/m² BD plus weekly oxaliplatin 50-60 mg/m² during radiotherapy course. Radiotherapy was delivered by 4500-5000cGy/25-28f with 3D conformal planning for 25-28 sessions for five to six weeks, and at the same time oral 5-FU and weekly injected Eloxatin during six weeks were administered. Six to eight weeks after neoadjuvant chemoradiation therapy, all patients underwent surgery by one expert oncologist surgeon. After surgery, the patients were evaluated from the viewpoints of margin and complete response and the state of sphincter-preservation as the result of the operation. The patients who had incomplete data record were excluded from the study. Collected data were analyzed by SPSS software 14 with descriptive statistics.

Results

Seventy patients with the cancer of rectum who were under treatment at this center enrolled the study from the year 2005 up to 2010. They included 50 men (71.5%) and 20 women (28.5%). The age range was 16- 85 years old with the highest age frequency of 66- 75 years (25%). From this number, seven persons had a complete response (10%) that is, they had a pathologic complete response and no tumor cells were found in the surgical specimens. Of 70 patients who had neoadjuvant chemoradiation therapy during this period, 42 persons had a negative surgical margin (60%), in other words; the anastomosis margin had no tumor cell. In other patients, the surgical margin was involved (40%). Among marginal involved cases, 24 and 4 persons had APR and LAR, respectively. Finally, from 70 patients who had neoadjuvant therapy during 2005-2010, 40 persons (57%) had sphincter- preservation after the surgery; there was no need for conducting permanent colostomy so with better quality of life for patient. In addition, the rates of sphincter- preserving followed by the considered protocol of this study in cases that the distance of the tumor from the anal verge was five cm or more and in cases with the distance less than 5 cm were 51.4% and 5.6%, respectively.

Discussion

As we enter the 21st century, cancer of the rectum has become an important social and medical problem. Nowadays, cancer of the rectum accounts for about 30% of all the colorectal cancers (5, 9). Many benefits are mentioned for the use of neoadjuvant chemoradiation. Among them, one is the possibility of performing chemotherapy by radiation with higher dosages and the other is downstaging of the tumor (60-80%) and also reaching a pathologic complete response (15- 30%) and the ability to shrink the tumor which facilitates the surgical resection of the tumor and on the other hand, the permission of achieving a negative margin and performing sphincter-preserving operation. The other benefit is that the radiation is well radiated to the tissue which have normal oxygenation instead of radiation to devascularized pelvic tissue after surgical dissection and radiation to the anastomosis, and also lower probability of causing radiation enteritis because small bowel is not in the pelvis (4-9).

The Dutch Colorectal Cancer Group has shown an important reduction in the rate of local relapse during two years in the patients who had preoperative radiotherapy combined with TME compared to those who had only TME (24% versus 8%). The Swedish Rectal Cancer Trial is the first and the only study, which has shown the survival benefit (58%) for the Dukes C patients receiving preoperative radiation (short period of five Gy of five days) and combined with operation compared to the patients who underwent only surgery (48%). In addition, a reduction in the relapsing rate was reported in the group treated by only radiation (11%) compared to the group treated by only surgery (27%) (5, 10).

Besides, a meta-analysis study showed that radiation treatment in addition to surgery prominently causes reduction in the 5- year mortality rate, the rate of mortality related to cancer, and the rate of local relapse compared to only surgery (10). Sauer designed a chemotherapy protocol before or after the surgery based on a long period of radiotherapy (5040 cGy in the fraction 180 cGy daily for five days in a week) and 5- FU (120 hours intravenous infusion during the first and the fifth week), simultaneously for the patients with the clinical stages II and III rectal cancer. After six weeks, TME was conducted and next four periods of 5- FU, was given one month after the operation. Finally, it was found that the four-year survival in the two groups did not have any difference. However, there was an important reduction in the local relapse (6% versus 13%), and toxicity in the patients treated with neoadjuvant protocol (11).

Neoadjuvant therapy has more successes in local control compared to adjuvant therapy. The two methods increase the overall survival. The shorter period versus long-term period of Radiotherapy (RT) is controversial. Radiation affects the sexual and anorectal function. The data show that neoadjuvant radiation causes lower toxicity compared to adjuvant radiation. In addition, short- term period has lower toxicity (12). In a study on 106 patients, the interval between CRT and surgery was seven weeks. Down staging was occurred on 78 patients (13).

Neoadjuvant chemoradiation may increase the operational ability to control continence by down staging. In some cases by shrinking the tumor, we can achieve a cancer- free margin in the distal part of the resection which without shrinkage we cannot reach anastomosis in a safe margin (11). According to the conducted research, the rates of pathologic complete response (10%), clear surgical margin in sphincter-preservation on the condition of distance of the tumor from anal verge five cm or more than five cm (51%) and on the condition of distance less than five cm sphincter preservation were (5.6%) and overall negative surgical margin were 60%. In the previous studies, the rate of pathologic complete response was reported 15- 30 % (9). In the conducted study, by pathologic complete response in seven patients and probably down staging in other cases, outcome of patients will be better.

In one study, after a short-term radiation of five days before the operation, the survival benefit was 58%. Although if it was not received by only surgery, it would be 48 % (12). In the conducted research, the anal sphincter was preserved in those who had a rectal tumor with the distance more than five cm of the anal verge, which this means avoidance from colostomy and its special complications. In the performed research, the rate of clear surgical margin is 42%, which this means first, avoidance of again operation, decrease of the probability of short- term local relapse, and finally will raise overall survival of the

patients. In a similar study, a reduction in the rate of the local relapse was shown in the group receiving radiation (11%) compared to the group having only-surgery (27%) (9).

Conclusion

According to this study we concluded neoadjuvant chemoradiation in stage II and III of rectal cancer may increase rate of operating with safe margin and in addition sphincter saving procedure be more achievable.

Acknowledgements

We appreciate and thank the Research Deputy vice-chancellor for research affairs of the Ahvaz Jundishapur University of Medical Sciences, especially the Research Consultation Centre(RCC) for technical support.

Conflict of Interest

There is no conflict of interest to be declared.

Authors' contributions

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

References

1. National Cancer Institute. Surveillance, Epidemiology, and End Results Program (SEER). Cancer Stat Facts: Colon and Rectum Cancer. Available at: <https://seer.cancer.gov/statfacts/html/colorect.html>
2. Ryan R, Gibbons D, Hyland JM, Treanor D, White A, Mulcahy HE, et al. Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. *Histopathology*. 2005;47(2):141-6.
3. Ansari R, Mahdavinia M, Sadjadi A, Nouraei M, Kamangar F, Bishehsari F, et al. Incidence and age distribution of colorectal cancer in Iran: results of a population-based cancer registry. *Cancer letters*. 2006;240(1):143-7.
4. Capirci C, Valentini V, Cionini L, De Paoli A, Rodel C, Glynn-Jones R, et al. Prognostic value of pathologic complete response after neoadjuvant therapy in locally advanced rectal cancer: long-term analysis of 566 ypCR patients. *International Journal of Radiation Oncology Biology Physics*. 2008;72(1):99-107.
5. Kapiteijn E, Marijnen CA, Nagtegaal ID. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med*. 2001; 345:638–646.
6. Kapiteijn E, Van De Velde CJ. The role of total mesorectal excision in the management of rectal cancer. *Surg. Clin. North Am*. 2002; 82(7) 995–1007.
7. Cedermark B, Dahlberg M, Glimelius B, Pahlman L, Rutqvist LE, Wilking N. Improved survival with preoperative radiotherapy in resectable rectal cancer. *NEJM*. 1997;336(14):980-7.
8. Russo S, Steele S, Fredman E, Biswas T. Current topics in the multimodality treatment of locally advanced rectal cancer. *Future Oncology*. 2016;12(7):963-79.
9. Zinner MJ, Ashley SW: *maingot's abdominal operations*. 11th ed. Boston, McGraw-Hill com, 2007
10. Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in respectable rectal cancer. *N Engl J Med*. 1997; 336:980–987.
11. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemo radiotherapy for rectal cancer. *N Engl J Med*. 2004; 351:1731–1740.
12. Eich HT, Stipien A. Neoadjuvant radiochemotherapy and surgery for advanced rectal cancer: Prognostic significance of tumor regression, *strahlentheronkol*. 2011. 187(4); 225-230.
13. Popek S, Tsikitis V. Neoadjuvant vs. adjuvant pelvic radiotherapy for locally advanced rectal cancer: Which is superior? *World j Gastroenterol*. 2011; 17(7): 848–854.