# Survival outcome and pathologic complete response of patients suffered from the local advanced rectal cancer treated with Neo-adjuvant Chemo-radiation


## Abstract

At present, neo-adjuvant chemo-radiation and following that surgery are considered as a care standard in local advanced rectal cancer. We retrospectively investigated disease-free survival [1] and pathologic complete response [2] in patients suffered from advanced rectal cancer. The medical case history of 531 patients suffered from advanced rectal cancer (T3/T4 or N+) who had been treated at Imam Hussein Hospital from 2008 to 2019, was investigated to record the data set after the Institutional Review Board [3] confirmation. The age average of the patients was 57.37 years old with a changes range of 24-90 years old and 58.2% of the patients were men. Starting the patient's therapy was with radiotherapy along with 5FU for 5-6 weeks, and about 8-12 weeks after the completion of concurrent chemo-radiotherapy, patients received surgery and following that adjuvant chemo-therapy with the 5FU basal regimen every two weeks. Demographic and clinical information of the patients, pathological complete response (PCR) rate, and disease-free survival (DFS) were recorded. The results indicated that neo-adjuvant chemo-radiation led to the declining the tumor stage in 73.5% of patients and the sphincter was preserved in a great number of patients (71.9%). One, three- and five-year-old DFS of patients were determined as 85%, 77% and 59%, respectively. The PCR rate of patients was 11.5%.



**Key words:** rectal cancer, neo-adjuvant chemo-radiation, pathologic complete response, disease-free survival.


## Introduction

Colorectal cancers are as one of the main reasons for death caused by cancer in the world and its incidence is increasing in Iran during the last 25 years. Colorectal cancers are the third prevalent cancer among Iranians after breast and stomach

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[1] بقای عاری از بیماری
[2] پاسخ کامل پاتولوژیک (آسیب شناسی)
[3] هیئت بررسی سازمانی

cancers according to the Iran's 2014 data, so that its annual incidence is more than 7100 cases per year (1).

The outcome has significantly improved for patients suffered from rectal cancer over the last 30 years. Previously, local recurrences of the pelvis were occurring in more than one-third of patients suffered from apparently local tumors. Total meso-rectal excision [4] was the first step to improve local control by a reducing the local recurrences to less than 5% (2). However, surgery has disadvantages, including stimulating growth factors and suppressing the immune system, which may increase tumor progression and the micro-metastases spread in the post-operative [5] environment (3).

The second step was pre-operative [6] radiotherapy in both short and long term along with the simultaneous administration of chemo-therapy, which reduced local recurrences to the minimum possible even in local advanced tumors that surgery was not possible or they were not treatable (2). Neo-adjuvant chemo-radiation is now a care standard treatment for local advanced diseases (T3/4 or N+) (4).

Primary neo-adjuvant chemo-radiation has benefits, including extirpation [7] of circulating tumor cells and lymph nodes metastases, tumor shrinkage, and reduction of tumor cell-shedding due to surgical trauma (5-8). Also, surgery after neo-adjuvant chemo-radiation can remove the tumor more radically and increase the minimum possible access (5). In numerous studies, a significant improvement has been reported in recurrence and 5-years survival rate of patients suffered from rectal cancer in pre-operative co-radiation in comparison with surgery alone or surgery and post-operative radiations (9, 10).

As expressed, neo-adjuvant chemo-radiation is a standard therapy for patients suffered from clinical stage II and III rectal cancer. Nevertheless, the benefits of post-operative adjuvant chemo-therapy are indistinctive for patients after neo-adjuvant chemo-radiation. On the other hand, considering the high prevalence of colorectal cancer in the Iranian population, our knowledge about the clinical features and patients' survival is limited (11-14). In this study, clinical features and

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[4] برداشتن کامل مزورکتال
[5] بعد از عمل
[6] قبل از عمل
[7] ریشه‌کنی

survival parameters have been described in patients suffered from local advanced rectal cancer treated with neo-adjuvant chemo-radiation. The results of this study can be helpful in planning for screening and follow-up patients suffered from rectal cancer.

## Method

## Selecting patients

We investigated patients suffered from local advanced rectal cancer at Imam Hussein Hospital, Tehran (Iran) in a retrospective consecutive cohort study, between 2008 and 2019. If patients had T3-T4 stage or positive lymph nodes by confirmation of a CT scan, endo-rectal ultrasound[8], colonoscopy, PET-CT and MRI, they were included in the study. Patients with incomplete file information were excluded from the study. Eventually, 531 patients were included in the study.

## Treatment

Starting the patient's treatment has been with radiotherapy, and was accompanied by concurrent chemo-therapy based on 5FU, which treatment was done for 5-6 weeks. Surgery was planned for patients between 8 to 12 weeks after completion of concurrent chemo-radiotherapy. The type of surgery was based on the selection of the surgeon. 8 to 12 weeks after surgery, patients underwent adjuvant chemo-therapy with the 5FU basal regimen [9] every two weeks up to 8 courses.

## Follow up

After the surgery, the routine follow-up evaluation of the patients was done once every 3 months for 3 months and then twice a year for 5 years. CT scan of the chest, abdomen and pelvis was done at each visit and the patients were evaluated in terms of recurrence in the pelvis and recurrence of outside the pelvis.

### Pathologic examination and performance evaluation

Patients were investigated in terms of grade and stage T and N of the tumor. The transverse section of the removed sample of all patients was evaluated by a

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[8] سونوگرافی اندورکتال
[9] رژیم پایه

surgical pathologist after staining [10] using hematoxylin and eosin. PCR of patients was defined as the absence of viable cancer cells in the intestinal wall and mesoctoma (pT0N0). The primary endpoint was disease-free survival time. Secondary endpoint was the rate of PCR and adverse complications[11].

## Data analysis

Data were analyzed using SPSS software (version 22). Description of quantitative variables was performed by mean and standard deviation and description of qualitative variables was performed by number and percentage. Disease-free survival rate was evaluated using the Meier- Kaplan curve and using the Log Rank model.

## Findings

In this study, we assessed 531 patients suffered from advanced rectal cancer from 2008 to 2019. The age average of the patients was 58 years old and the age range was 41-79 years old. 58.2% of patients were men. 61.1%, 30.4%, and 8.6% of patients were grade I, II, and III, respectively.

Before treatment,the T stage distribution of the disease included 0.8% T1, 12.6% T2, 75.5% T3, and 11.1% T4 that after surgery, it improved to 24.8% T1, 24% T2, 26.7% T3, and 2.3% T4 and tumor growth was not observed in 22.1% of patients (T0). Also, before surgery, the tumor lymphatic stage included 29.7% N0, 51.8% N1, 16.7% N2, and 1.8% N3, and after surgery, it included 53.9% N0, 36.8% N1, and 9.3% N2 (Table 1). Pathologic reduction of both T and N stages was investigated and, as a result, response to reduced tumor stage was defined by pre-operative chemo-radiation. For this reason, reducing the chemo-therapy dose was performed during the treatment period in less than 10% of patients. Thus, reducing the dose was not an effective factor in the tumor pathologic evaluation and the tumor stage change. The evidence indicated that the stage of about 73.5% of patients was reduced. The disease extent remained stable in 22.2% of patients and tumor progression was observed in 4.3% of patients alone.

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[10] رنگ آمیزی
[11] عوارض جانبی

In our study, survival evaluation parameters included DFS and PCR in patients. Recurrence was observed in 142 patients during the study period, and 2-years, 3-years, and 5-years-old DFS were determined as 85%, 77%, and 59%, respectively (Figure 1). PCR of patients was 11.5% (53/458) (Table 1).

**Table 1-** Describing the demographic and clinical information of patients

| **Variable** | | **N(%) or mean** |
|---|---|---|
| Age (year)<br>N=531 | - | 57.37<br>(24, 90) |
| Gender<br>N=531 | Male | 309(58.2) |
| | Female | 222(41.8) |
| Grade<br>N=303 | I | 185(61.1) |
| | II | 92(30.4) |
| | III | 26(8.6) |
| Pre operation T<br>N=486 | I | 4(0.8) |
| | II | 61(12.6) |
| | III | 367(75.5) |
| | IIII | 54(11.1) |
| Post operation T<br>N=475 | 0 | 105(22.1) |
| | I | 118(24.8) |
| | II | 114(24) |
| | III | 127(26.7) |
| | IIII | 11(2.3) |
| Pre operation N<br>N=276 | 0 | 82(29.7) |
| | I | 143(51.8) |
| | II | 51(18.5) |
| Post operation N<br>N=492 | 0 | 265(53.9) |
| | I | 181(36.8) |
| | II | 46(9.3) |
| Harvestd N<br>N=470, (min, max) | - | 8.64<br>(0, 26) |
| Involved N<br>N=475, (min, max) | - | 1.43<br>(0,12) |
| Margin<br>N=476 | Negative | 465(97.7) |
| | Positive | 11(2.3) |
| Sphincter saving<br>N=288 | yes | 207(71.9) |
| | no | 81(28.1) |
| PCR (%)<br>N=458 | - | 53(11.5) |

**Figure 1-** Graph [12] of survival probability function [13] (month) in patients suffered from local advanced rectal cancer

## Discussion

The age average of the patients was 57.37 years old in our study. Other performed Iranian studies in different areas that were investigating patients suffered from rectal cancer, reported the age average of patients as 60.8 years old (11) and 54.48 years old (12), which is consistent [14] with the present study and shows that the prevalence age of this cancer is in the range of 50-60 years old in the Iranian population. The prevalence rate of local advanced rectal cancer was 58.2% in men and was higher than in women (41.8%), which is consistent with the reported results in other Iranian studies (11 and 12).

The results indicated that reducing the tumor stage occurred in 73.5% of patients by neo-adjuvant chemo-radiation, which this procedure led to a high rate of tumor extirpation and sphincter preservation in patients. During the last decade, neo-adjuvant chemo-radiation and following that surgery has become the care standard for local advanced rectal cancer, which leads to local control improvement without effect on long-term survival (15). A similar study to ours has confirmed in many studies that neo-adjuvant chemo-radiation reduces the pathologic stage of rectal cancer and causes the absence of adenocarcinoma cells in the post-operative sample (T0 N0 M0) (16-19).

In our study, survival evaluation parameters included PCR and 1-, 3-, and 5-years disease-free survival. The results showed that the PCR rate was 11.5% in patients. A similar Iranian study on investigating the PCR of patients suffered from local advanced rectal cancer was not found. Generally, the PCR rate in the effectiveness of neo-adjuvant chemo-radiation has been reported as 10-32% (20-22) in the performed studies, which is consistent with our study. Although the PCR effect on patients survival was not evaluated in our study, numerous studies have indicated that there is a better result in PCR by pre-operative therapy, and PCR is an important variable in the patients survival suffered from local advanced rectal cancer (23-25). It was estimated that 1-, 3-, and 5-years disease-free survival is

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[12] گراف، نمودار
[13] تابع
[14] همسو، مطابق

85%, 77%, and 59% in patients, respectively. Researches of similar studies in the Iranian population indicated that 1-, 3-, and 5-years disease-free survival was 97%, 88%, and 55%, respectively (11) and the 5-years survival rate was 52% in the meta-analysis study of Panahi et al. (2019) (13). It has been reported that the 5-years disease-free survival rate of patients suffered from colorectal cancer is lower in our country than in developed areas, which is the most important factor of the disease diagnosis in advanced stages (14).

There were several limitations to this study. Totally patients survival was not evaluated in our study. Other limitation was the incompleteness of the patient's file information and not investigating the treatment compliance of the study.

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