

Three Perspectives: The Approach of Neoadjuvant Treatment of Rectum Cancer According to Medical Oncologists, Radiation Oncologists, and Surgeons

Ismail Beypinar (✉ ibeypinar@yahoo.com)

Eskisehir City Hospital

Mustafa Tercan

Eskisehir City Hospital

Fuzuli Tugrul

Eskisehir City Hospital

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Abstract

Purpose

Two treatment options are considered for radiotherapy: short-course radiotherapy and immediate surgery or chemoradiation with 5-Fluorouracil based chemotherapy with delayed surgery. We try to evaluate the real-life treatment approaches of medical, radiation, and surgical oncologists for neoadjuvant treatment of rectal cancers.

Method

The online survey form was established via Google Forms. The survey was taken voluntarily by medical oncologists, radiation oncologists, surgical oncologists, and general surgeons.

Results

One hundred eighty-three of the participants were medical oncologists while 36 were radiotherapists and 36 were surgeons. Most of the study population preferred long-course radiation therapy and chemotherapy (85%). Two-thirds of the participants preferred chemotherapy before operation. The most frequent chemotherapy cycles for the pre-operative setting were 'three' or 'four-or-more'. (27,8% and 25,1% respectively) Medical oncologists had a significantly higher tendency of offering chemotherapy between radiation therapy and surgery compared with the other groups. The optimal time of surgery was different between groups. There was no difference among groups between surgery and the 'watch & wait' strategy. Neoadjuvant chemotherapy regimens were different between groups significantly.

Conclusion

We found the new pre-operative chemotherapy regimen with short-course radiotherapy was slowly adopted in current practice. Also, medical oncologists tend pre-operative chemotherapy compared with other groups.

Introduction

Chemoradiation (CRT) is the gold standard of care in newly diagnosed rectal cancers.[1] The main objective of the treatment is to improve surgical outcomes, prevent local recurrence, prolong disease-free (DFS) and overall survival (OS). Two treatment options are considered for radiation therapy: short-course radiotherapy (RT) and immediate surgery or chemoradiation with 5-Fluorouracil (5-FU) based chemotherapy (CT) with delayed surgery.[1, 2] Especially in controversial areas, the initial treatment plan is mainly depending on the decision of the treating physician.[3] Two treatment options have similar results in terms of survival, R0 surgery, distant and local recurrences. Pathological complete remission (pCR) rates are higher in long course radiotherapy in combination with CT.[4] The local and distant recurrence rates were favoring CR after CRT compared with non-responders after surgery.[5] Prior studies showed that the addition of multidrug (only oxaliplatin-containing) regimens was not related to increased

pCR but resulted in higher rates of toxicity. A modest benefit was observed with the addition of oxaliplatin to 5-FU and radiation.[6]

Rectal cancers with mid or low location (infraperitoneal) which are T3-4 or with nodal metastasis, are recommended to receive CRT by current guidelines. Also, circumferential resection margin (CRM) involvement is an indication for neoadjuvant treatment. Possible total neoadjuvant treatment may be offered to current guidelines including the FOLFOXIRI regimen.[7] Although CRT was associated with decreased local recurrence, no improvement was observed in OS.[1, 8] CRT mainly resulted in downsizing in the majority of the patients (70%), even less with a pCR (20%). The pCR group is related to a good prognosis and has an excellent OS of over 90%.[9] Although small tumors have a better response to CRT, there are multiple controversial factors determining CRT response. The optimal interval after CRT to surgery is still unknown. The Lyon trial compared 2 weeks delay with 6 weeks after CRT which resulted in increased pCR and near pCR rates.[10] The main objective of the delay after CRT depends on the delayed lysis of the tumor cells after immediate DNA damage with CRT. The tumor cells were reported to be morphologically intact shortly after RT.[11, 12] Multiple studies evaluated the optimal time for the surgery after CRT, but there was no correlation between studies.[13–15]

In a Canadian study evaluating the surgical attitudes on rectal cancer, the waiting period after CRT was mostly determined to be 6 weeks. Also, low numbers of the 'Watch & Wait' strategy were observed. This study was mainly focused on surgical techniques, not the selection of the type of treatment. Different surgical types were investigated in this study such as microscopic anal resection or total mesorectal surgery.[16] Also, a survey study was performed in the Netherlands to acquire information about the preferences and awareness of surgeons, especially in lateral lymph nodes status.[17]

In radiological studies, the tumor position, maximum distance from the anal verge, maximum tumor length, thickness, area, and volume were evaluated. These factors were reported to be a directive marker for pCR except for tumor thickness.[18] Different treatment preferences especially in controversial areas in colon cancer were previously studied.[19, 20]

In this study, we try to evaluate the real-life treatment approaches of medical, radiation, and surgical oncologists for neoadjuvant treatment of rectal cancers.

Materials And Methods

Participants

An online survey link was sent to the medical oncologists, radiation oncologists, and surgeons via e-mail and mobile applications. The survey was started on 1st November 2021 and ended on 29th November 2021. The survey was sent to all oncologists, radiotherapists, and surgeons registered to their professional association in Turkey.

Survey

The online survey form was established via Google Forms. The survey was answered voluntarily by medical oncologists, radiation oncologists, surgical oncologists, and general surgeons. At the beginning of the questionnaire, the participants were informed that their preferences in rectal cancer treatment would be evaluated. Their consent was acquired at the start of the survey. The participants were informed to answer the questions in optimal conditions such as treatment options and imagining methods. The survey was containing 14 questions that were designed to understand the participants' experience, working conditions, and rectal cancer treatment decisions. Two questions were mandatory for medical oncologists, not the other participants. Information about the experience in oncology practice, academic status, and the type of hospital was obtained from the participants. All questions were mandatory to answer.

Statistical Analyze

The survey results were analyzed using descriptive statistics, and Chi-square tests were used to calculate the p values with SPSS version 21.0. Also, e-PICOS was used to analyze the difference between percentages by Z-test. The level of significance was determined as $p < 0.05$.

Ethics

The study was carried out by the Declaration of Helsinki principles and all applicable regulations. The participants declared they fill the form voluntarily. There were no promotions or gifts to increase participation.

Results

The numbers of recipients for each group including medical oncologists, radiotherapists, and surgeons were 867, 248, and 217 respectively. A total number of 255 participants responded to the survey. One hundred eighty-three of the participants were medical oncologists while 36 were radiotherapists and 36 were surgeons. Nineteen of the surgeons were surgical oncologists and while 17 were general surgeons. The ages of the participants were mostly between 30 to 40 years. (61,2%) Nearly fifty percent of the participants had less than 5 five-year of experience in oncology practice. Most of the study population was fellows and specialists with a cumulative percentage of 75. Forty-six percent of the answerers were working in university hospitals. Nearly fifty percent of the participants had examined 5 or fewer newly diagnosed rectal cancers. Most of the study population preferred long-course radiation therapy and chemotherapy. (85%) Two-thirds of the participants prefer chemotherapies before operation. The most frequent chemotherapy cycles for the pre-operative setting were 'three' or 'four-or-more'. (27,8% and 25,1% respectively) Forty percent of the participants preferred the XELOX protocol. Fifty-four of the medical oncologists prefer adjuvant chemotherapy even if the patient had complete remission after neoadjuvant

treatment. Nearly half of the study participants considered the 7th and 8th weeks to be the optimal time for surgery. Most of the study population prefer surgery even if the patient had complete remission after neoadjuvant treatment. (82%) The features of the study population were described in Table-1.

Table-1: Features of the study population

<i>Profession</i>	<i>Medical oncologists</i>	<i>Radiation oncologists</i>	<i>Surgeon</i>		
<i>N (%)</i>	184 (72,2)	36 (14,1)	35 (13,7)		
<i>Age (years)</i>	30-40	41-50	51-60	61-70	
<i>N (%)</i>	156 (61,2)	77 (30,2)	18 (7,1)	4 (1,6)	
<i>Experience (years)</i>	5 or less	6-10	11-20	21-30	
<i>N (%)</i>	122 (47,8)	49 (19,2)	67 (26,3)	17 (6,7)	
<i>Position</i>	Fellow	Specialist	Assoc. Prof	Professor	
<i>N (%)</i>	97 (38)	95 (37,3)	31 (12,2)	32 (12,5)	
<i>Facility</i>	State H.	Res. & Edu H.	University H.	Private H.	
<i>N (%)</i>	21 (8,2)	81 (31,8)	118 (46,3)	32 (12,7)	
<i>(Monthly) Rectal Cancer</i>	5 or less	6-10	11 or more		
<i>N (%)</i>	123 (48,2)	91 (35,7)	41 (16,1)		
<i>Neo-adj treatment</i>	Short-course	Long-course +CT			
<i>N (%)</i>	37 (14,5)	218 (85,5)			
<i>Neo-adj CT</i>	Yes	No			
<i>N (%)</i>	157 (61,6)	98 (38,4)			
<i>Neo-Adj Cycles</i>	0	1	2	3	4 or more
<i>N (%)</i>	40 (15,7)	50 (19,6)	30 (11,8)	71 (27,8)	64 (25,1)
<i>Type of CT</i>	None	Capecitabine/5-FU	XELOX	Folfox	
<i>N (%)</i>	62 (24,3)	35 (13,7)	102 (40)	56 (22)	
<i>Optimal time for Surg.</i>	6 w. or before	7-8 w.	9-10 w.	11-12 w.	13 w or later
<i>N (%)</i>	43 (16,9)	122 (47,8)	38 (14,9)	48 (18,8)	4 (1,6)
<i>CR strategy</i>	Surgery	Watch & wait			
<i>N (%)</i>	210 (82,4)	45 (17,6)			

H: Hospital; Res. & Edu. H.: Research and Educational Hospital; CT: Chemotherapy; Neo-Adj: Neo-Adjuvant; 5-FU: 5-Fluorouracil; XELOX: Oxaliplatin plus Capecitabine; Folfox: Oxaliplatin, Leucovorin, 5-Fluorouracil; W.: Week; CR: Complete Remission

There was a difference between age groups in terms of specialization which showed medical oncologists had a younger age comparing other branches. ($p < 0,001$) Also, medical oncologists significantly had less experience when compared with radiation oncologists and surgeons. ($p < 0,001$) There were no fellows in radiation oncology and surgeon groups, which was nearly fifty percent in the medical oncology subset.

($p < 0,001$) There was no difference between groups using short or long-course radiation plus chemotherapy. ($p = 0,09$) Medical oncologists had a significantly higher tendency of offering chemotherapy between radiation therapy and surgery compared with the other groups. ($p < 0,001$) The optimal time of surgery was different between groups. ($p = 0,006$) (Table-2)

Table-2: The optimal operation time according to groups.

<i>Time of Surgery</i>	<i>Medical Oncologists</i>	<i>Radiation Oncologists</i>	<i>Surgeon</i>
<i>6 w of before</i>	36 (a)	2 (a)	5 (a)
<i>7-8 weeks</i>	93 (a)	16 (a)	13 (a)
<i>9-10 weeks</i>	21 (a)	12 (b)	5 (a, b)
<i>11-12 weeks</i>	30 (a)	6 (a, b)	12 (b)
<i>13 w or after</i>	4 (a)	0 (a)	0 (a)

**Different letter shows statistical significance between groups in post-hoc analysis*

Also, the decision of optimal time of surgery evaluated among surgeons was not different between surgical oncologists and general surgeons favoring 7-8 weeks and 11-12 weeks at the same degree. ($p = 0,98$) Forty-two percent of the surgeons declared they will use neoadjuvant chemotherapy between CRT or short-term radiotherapy and surgery. The utility of chemotherapy cycles was equal in '3' and '4 or more' as 17,1% among surgeons. Fifty-one percent of the surgeons do not offer chemotherapy until the time of the surgery. There was a significant difference between groups in posthoc analysis. (Table-3)

Table-3: The offered chemotherapy cycles before surgery according to groups.

<i>Offered Cycles</i>	<i>Medical Oncologists</i>	<i>Radiation Oncologists</i>	<i>Surgeons</i>
<i>0</i>	0 (a)	22 (b)	18 (b)
<i>1</i>	47 (a)	0 (b)	3 (a, b)
<i>2</i>	20 (a)	8 (a)	2 (a)
<i>3</i>	63 (a)	2 (b)	6 (a, b)
<i>4 or more</i>	54 (a)	4 (a)	6 (a)
<i>Total</i>	184	36	35

**Different letter shows statistical significance between groups in post-hoc analysis*

There was no difference among groups between surgery and the 'watch & wait' strategy. ($p = 0,11$) A significant difference was observed between groups in offered neoadjuvant chemotherapy regimens. ($p < 0,001$) (Table-4)

Table-4: The offered chemotherapy regimens according to groups.

<i>Offered Regimen</i>	<i>Medical Oncologists</i>	<i>Radiation Oncologists</i>	<i>Surgeons</i>
<i>Capecitabine/ 5-FU</i>	17 (a)	5 (a, b)	13 (b)
<i>XELOX</i>	93 (a)	8 (b)	1 (c)
<i>Folfox</i>	45 (a)	3 (a)	8 (a)
<i>None</i>	29 (a)	20 (b)	13 (b)

**Different letter shows statistical significance between groups in post-hoc analysis, 5-FU: 5-Fluorouracil; XELOX: Oxaliplatin plus Capecitabine; Folfox: Oxaliplatin, Leucovorin, 5-Fluorouracil*

Discussion

In our study, we evaluate similarities and differences in neoadjuvant treatment of rectal cancer according to radiotherapists, medical oncologists, and surgeons. The ultimate goal for neo-adjuvant treatment is CR which can be achieved in different treatment models for different risk stratification.

In patients who had pCR after neoadjuvant CRT, long-term outcome was reported to be excellent with less local and distant recurrence. The pCR rates were considered to be between 15-27% after neoadjuvant CRT and delayed surgery.[21] Although pCR is considered to be good prognostic factor 5 years OS is still the main determiner in this patient group.[22] Valentini et al showed that 2 years' DFS considered to be a better prognostic factor than pCR in rectal cancer.[23] The clinic utility of the pCR is still controversial and needs to be investigated. In contrast to other studies, our study population was formed by high numbers of CR patients, which established a valuable source of information in this patient group. Also, the study may be valuable for future meta-analysis.

The response to the CRT may have a relation with the delay of surgery.[24] The first strong study was the Lyon study showing six weeks of delay until the surgery increased the pCR in patients compared to two weeks.[25] In a large study, 10-11 weeks delay of surgery after neoadjuvant CRT have the highest pCR rates. No increased response rates were observed with waiting longer than this time interval.[26] Retrospective data reported prolonging the interval between CRT and surgery increasing the CR rates. Moore et al and Tulchinsky et al. declared waiting more than 7 weeks increased the CR rates significantly. [24, 27] Another study confirmed the prior studies with an eight-week waiting period. The CR rates were doubled with a longer interval.[28] This data was strengthened with a meta-analysis that was performed in 2005. Better outcomes and CR rates were reported without significant morbidity.[29] On the other hand, waiting longer than 11 weeks did not result in a favorable outcome. Comparing 7 weeks to 11 weeks interval between CRT and surgery was failed to show increased CR rates.[30] Similar to our results in a Turkish population study there was no difference between 4 and 8 weeks' waiting period between CRT and surgery.[31] In our study, we showed most of the participants had preferred 7-8th and 11-12th weeks were the optimal operation period. Although the hypothesis of a longer waiting period increased the CR

rates the optimal duration of the interval is not firmly established. A very small subset of the study population declared, they prefer to perform surgery more than the 13th week. Also, the effect of genetic and racial differences on tumor response is not known. The confirmative results of Saglam et al. may strengthen the racial effect on tumor response in the Turkish population.[31] Our findings were substantially identical to the findings of the Canadian surgeon research in terms of optimal surgery time. [16] A higher rate of surgery before 6 weeks was seen in this trial, which might be related to short-course radiation treatment without chemotherapy. Also, there was no difference between surgeons, oncologists, and radiotherapists. A different trial which was based on a scenario-based questionnaire found a difference between decisions of the optimal time of surgery among surgeons, gastrointestinal oncologists, and radiotherapists. This study was focused only 6th and 8th weeks after CRT.[32]

The second controversial area is adding neoadjuvant chemotherapy to the treatment plan. Also, the optimal protocol and number of cycles are questionable. Garcia-Aguelar showed that adding two cycles of chemotherapy including 5-FU, oxaliplatin and leucovorin had increased the pCR rates up to 38%. In our study, more than 20% of the patients received neoadjuvant chemotherapy. There was no effect on the prognosis in terms of OS. Also, the chemotherapy protocols and cycles were not eligible.[33] The neoadjuvant chemotherapy preference was significantly high in medical oncologists when compared with surgeons and radiotherapists. In the study Lefevre et al., although there were differences according to groups, long-term CRT was preferred in the absence of contraindications. The addition of neoadjuvant chemotherapy was not a frequent option for three groups consisting of surgeons, gastrointestinal oncologists, and radiotherapists.[32] Compatible with our results Hazen et. al reported long-term CRT with or without radiation boost is the most preferred option in colorectal surgeons according to their study. This study was consisting of colorectal surgeons different from our study. [17]

The selection of the treatment strategy is mainly dependent on primary risk factors and post-surgical margins. In the very-low risk group which is evaluated with endoscopic ultrasonography, the main treatment option is considered to be primary surgery. In patients with low-risk short-course, RT and conventional long-course radiotherapy with concurrent chemotherapy have similar results.[34] However, recent data published if the post-operative margin is at risk conventional treatment had similar results with short-course radiotherapy followed by pre-operative oxaliplatin including chemotherapy.[35] The difference between medical oncologists and other groups may depend on altered recurrence concerns in groups. In a study investigating treatment preferences of radiation oncologists, most of the physicians still prefer long-course radiation therapy. Short-course radiation therapy was mainly preferred in patients who are not a candidate for chemotherapy or social barriers for long-course treatment.[36]

The 'Watch & Wait' strategy was less frequently selected in our study group. (17%) The study which was published by Crawford et al., found 4.6 percent of participants select 'Watch & Wait', nearly 54.6 percent declared case by case strategy selection while 40.9 percent favored surgery.[16] In a study investigating radiation oncologists, the 'Watch & Wait' strategy was consisting 46 percent in correlation with the OnCoRe trial.[37]

Limitations

The study was a survey study that tries to evaluate the pitfalls but was still lacking revealing most of the unidentified parts in daily practice. The study was designed to evaluate routine practice and hybrid methods in the treatment of rectal cancer which may lack enough quality to determine special situations such as total neo-adjuvant treatment, CRM positivity, or utility of neoadjuvant chemotherapy regimens such as FOLFOXIRI. The participants from radiotherapists and surgeons were lesser compared with medical oncologists which made comparison hard between groups. Also, high numbers of young participants in the medical oncology group may affect the results, this phenomenon was a result of an increased quota of medical oncology compared to surgical and radiation oncology. There were limited data in literature comparing medical oncologists, radiation oncologists, and surgeons which made comparison difficult with other studies.

Conclusion

In our study, we found the new pre-operative chemotherapy regimen with short-course radiotherapy was slowly adopted in current practice. Also, medical oncologists tend pre-operative chemotherapy compared with other groups. The optimal surgery time for patients receiving neoadjuvant treatment is still controversial.

Learning Points

Medical oncologists are more prone to up-front chemotherapy in rectal cancer.

Total neo-adjuvant treatment is not a highly-selected option.

Medical oncologists offer more chemotherapy cycles before surgery.

'Watch & Wait' strategy is still not an option for all groups.

Declarations

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Ismail Beypinar: Idea, Concept, Manuscript Writing, Statistical Analysis **Mustafa Tercan & Fuzuli Tugrul:** Data Collection, Revision, Literature Search

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