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

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Abstract

Purpose

Two treatment modalities are considerable for radiation therapy: short-course radiotherapy and immediate surgery or chemoradiation with 5-Fluorouracil based chemotherapy with delayed surgery. In this study, 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 which was consisting eighty-five percent. Two-thirds of the participants apply chemotherapies before operation. The most frequent chemotherapy cycles for the pre-operative setting were ‘three’ or ‘four-or-more’ with the percent of 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. A significant difference was observed between groups in offered neoadjuvant chemotherapy regimens.

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.

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 modalities are considerable 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 modalities 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. Although CRT was associated with decreased local recurrence, no improvement was observed in OS.[1, 7] 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%.[8] 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.[9] 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.[10, 11] Multiple studies evaluated the optimal timing for the surgery after CRT, but there was no correlation between studies.[12–14]

In radiological studies, the tumor position, maximum distance from the anal verge, maximum tumor length, thickness, area, and volume were evaluated. These factors except tumor thickness were reported to be a directive marker for pCR.[15] Different treatment preferences especially in controversial areas in colon cancer were previously studied.[16, 17]

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.

Survey

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

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 consisting 61,2 percent of the study population. 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 which was consisting eighty-five percent. Two-thirds of the participants apply chemotherapies before operation. The most frequent chemotherapy cycles for the pre-operative setting were ‘three’ or ‘four-or-more’ with the percent of 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 to operation. Eighty-two percent of the study population prefer surgery even if the patient had complete remission after neoadjuvant treatment. The features of the study population were described in Table-1.

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) 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)

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-3)

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.[18] Although pCR is considered to be good prognostic factor 5 years OS is still the main determiner in this patient group.[19] Valentini et al showed that 2 years' DFS considered being a better prognostic factor than pCR in rectal cancer.[20] 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.[21] 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.[22] 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.[23] 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. [21, 24] Another study confirmed the prior studies with an eight-week waiting period. The CR rates were doubled with a longer interval.[25] This data was strengthened with a meta-analysis that was performed in 2005. Better outcomes and CR rates were reported without significant morbidity.[26] 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.[27] Similar to our results in a Turkish population study there was no difference between 4 and 8 weeks' waiting period between CRT and surgery.[28] 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 the 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.[28]

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.[29] The neo-adjuvant chemotherapy preference was significantly high in medical oncologists when compared with surgeons and radiotherapists.

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.[30] 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.[31] The difference between medical oncologists and other groups may depend on altered recurrence concerns in groups.

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 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.

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.

Declarations

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Tables

Table-1: Features of the study population

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

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

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

**Different letter shows statistical significance between groups in posthoc analysis*

Table-3: The offered chemotherapy regimens according to groups.

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