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THREE PERSPECTIVES: THE APPROACH TO NEOADJUVANT TREATMENT OF RECTAL CANCER ACCORDING TO MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS, AND SURGEONS

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A – study design, **B** – data collection, **C** – statistical analysis, **D** – interpretation of data, **E** – manuscript preparation, **F** – literature review, **G** – sourcing of funding

ABSTRACT

Background: Two treatment options considered for radiotherapy are short-course radiotherapy and immediate surgery, or chemoradiation with 5-Fluorouracil based chemotherapy and delayed surgery.

Aim of the study: Evaluate the real-life treatment approaches of medical, radiation, and surgical oncologists, to neoadjuvant treatment of rectal cancers.

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

Results: Of those who participated, 183 were medical oncologists, 36 were radiotherapists, and 36 were surgeons. Most of the study population preferred long-course radiation therapy and chemotherapy (85%). Meanwhile, two-thirds of the participants preferred chemotherapy prior to operating. The most frequent chemotherapy cycles for the pre-operative setting were 'three' and 'four-or-more' (27.8% and 25.1%, respectively). Medical oncologists had a significantly higher tendency to offer chemotherapy between radiation therapy and surgery compared to the other groups. Optimal time of surgery was different between groups, but there was no difference among groups between surgery and the 'watch & wait' strategy. Neoadjuvant chemotherapy regimens were significantly different between groups.

Conclusions: We found that the new pre-operative chemotherapy regimen with short-course radiotherapy was slowly adopted into current practice. Also, medical oncologists tended to prefer pre-operative chemotherapy in comparison to the other groups.

KEYWORDS: chemotherapy, neoadjuvant treatment, radiotherapy, rectal cancer, treatment modalities

Background

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, and to prolong disease-free survival (DFS) and overall survival (OS). Two treatment options are considered for such radiation therapy, which includes short-course radiotherapy (RT) and immediate surgery, or CRT with 5-Fluorouracil (5-FU) based chemotherapy (CT) and delayed surgery.[1,2] In controversial areas in particular, the initial treatment plan is mainly dependent on the decision of the treating physician.[3] Both treatment options have similar results in terms of survival and resection margin 0 surgery

frequency, as well as distant and local recurrences. However, pathological complete response (pCR) rates are higher in long course RT in combination with CT [4]. Furthermore, local and distant recurrence rates favored complete remission (CR) after CRT compared with non-responders after surgery. [5] Prior research has demonstrated 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) that are at stage T3-4, or have nodal metastasis, are recommended by current guidelines to receive CRT therapy. Also, circumferential resection margin (CRM) involvement is an indication for neoadjuvant treatment. As such, total neoadjuvant treatment may be offered in addition to current guidelines, including the folinic acid, fluorouracil, oxaliplatin and irinotecan (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 patients (70%), though this was even less so in those with a pCR (20%). However, pCR was related to a good prognosis and an excellent OS of over 90%.[9]

Although small tumors have a better response to CRT, there are multiple controversial factors that determine the response to CRT. Indeed, the optimal interval after CRT to surgery is still unknown. This was investigated during the Lyon trial, which compared two weeks delay with six weeks delay after CRT, the latter of which resulted in increased pCR and near pCR rates.[10] The main reason for increasing the time to surgery after CRT is the delayed lysis of tumor cells after immediate DNA damage with CRT, with cells reported to be morphologically intact shortly after RT.[11,12] Multiple other studies have evaluated the optimal time for surgery after CRT, but no correlation was found between the studies.[13–15] In a Canadian study evaluating surgical attitudes to rectal cancer, the waiting period after CRT was mostly determined to be six weeks. Also, low numbers of the 'Watch & Wait' strategy were observed. The study focused mainly on surgical techniques used and not selection of the type of treatment. Different surgical types investigated in this study included microscopic anal resection and total mesorectal surgery.[16] Additionally, a survey based study was carried out in the Netherlands to acquire information about the preferences and awareness of surgeons, especially regarding lateral lymph nodes status.[17]

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

Aim of the study

To evaluate the real-life approaches of medical oncologists, radiation oncologists, surgical oncologists, and general surgeons, to neoadjuvant treatment of rectal cancers.

Material and methods

Study design and setting

An online survey form was established using Google Forms, and was answered voluntarily by medical oncologists, radiation oncologists, surgical oncologists, and general surgeons. Access to the survey commenced on 1st November 2021 and ended on 29th November 2021.

Participants

A link to the online survey was sent via e-mail and mobile applications to all oncologists, radiotherapists, and surgeons, who were registered to their professional associations in Turkey. Recipients of the survey included 867 medical oncologists, 248 radiotherapists, and 217 surgeons. A total of 255 recipients responded, 183 of which were medical oncologists, 36 were radiotherapists, and 36 were surgeons.

Survey

Consent was acquired from participants at the beginning of the survey and they were informed that their preferences in rectal cancer treatment would be evaluated. Participants were asked to answer questions on optimal conditions, such as treatment options and imagining methods. The survey contained 14 questions that were designed to understand the participants' experience, working conditions, and rectal cancer treatment decisions. Two questions were mandatory for medical oncologists, but were not required to be answered by the other participants. Answering all other questions was mandatory. Information about experience in oncology practice, academic status, and the type of

hospital in which they operate, was obtained from all participants.

Statistical analysis

Survey results were analyzed using descriptive statistics, and Chi-square tests were used to calculate p values, using SPSS® version 21.0 (IBM Corporation, NY, USA). Also, the difference between percentages was analyzed by Z-test using e-PICOS software (MedicRes, NY, USA). The level of significance was determined as $p<0.05$. No sample size evaluation was performed due to the survey nature of the study.

Ethics

The study was carried out according to the principles of the Declaration of Helsinki and all applicable regulations. Participants declared that they filled the form in voluntarily. There were no promotions or gifts offered to increase participation.

Results

The number of recipients for each group totaled 867 medical oncologists, 248 radiotherapists, and 217 surgeons. A total of 255 recipients responded to the survey, of which 183 were medical oncologists, 36 were radiotherapists, and 36 were surgeons. Nineteen of the surgeons were surgical oncologists and 17 were general surgeons. Participants were mostly aged between 30 to 40 years (61.2%) and almost half of them had less than five-years of experience in oncology practice. Most of the study population were fellows or specialists (75%), and there was a significant difference between oncologists, radiotherapists, and surgeons, in terms of experience. Indeed, medical oncologists had less experience in their field when compared to other specialists ($p<0.001$). Forty-six percent of respondents were working in university hospitals, and almost 50% had examined five or fewer newly diagnosed rectal cancers. Most of the study respondents preferred long-course radiation

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)	

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. Treatment preferences of the study population

Questions	Preferences				
Neo-adj treatment	Short-course	Long-course +CT			
N (%)	37 (14.5)	218 (85.5)			
Neo-adj CT	Yes	No			
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.

therapy and CT (85%). Two-thirds of the participants preferred CT prior to surgery, with the most frequent CT cycles in the pre-operative setting being 'three' and 'four-or-more' (27.8% and 25.1%, respectively). Forty percent of the participants preferred the oxaliplatin and capecitabine (XELOX) protocol, whilst 54 of the medical oncologists favored adjuvant CT, even if the patient had CR after neoadjuvant treatment. Nearly half of the study participants considered the 7th and 8th weeks to be the optimal time for surgery. Meanwhile, most of the study population favored surgery even if the patient had CR after neoadjuvant treatment (82%). Features of the study population are described in Table 1 and their main treatment preferences are described in Table 2.

There was a difference in age between groups in terms of specialization, with medical oncologists being of a younger age in comparison to other branches ($p<0.001$). Medical oncologists also had significantly less experience when compared with radiation oncologists and surgeons ($p<0.001$). Furthermore, there were no fellows in the radiation oncology and surgeon groups, which was nearly 50% of the medical oncology subset ($p<0.001$). There was no difference in the use of short or long-course radiation plus CT between groups ($p=0.09$). However, medical oncologists had a significantly higher tendency to offer CT between radiation therapy and surgery compared with the other groups ($p<0.001$).

The optimal time of surgery was different between groups ($p=0.006$) (see Table 3). However, the decision on optimal time of surgery among surgeons was not different between surgical oncologists and general surgeons, with both favoring 7-8 weeks and 11-12 weeks to the same degree ($p=0.98$). Forty-two percent of the surgeons declared that they use neoadjuvant CT between CRT or short-term RT and surgery. The utility of CT cycles was equal in terms of '3' and '4 or more' among surgeons, at 17.1%. Meanwhile, 51% of the surgeons did not offer CT until the time of surgery. There was a significant difference between groups in post hoc analysis (see Table 4). There was no difference among groups between surgery and the 'watch & wait' strategy ($p=0.11$). A significant difference was observed between groups in terms of the neoadjuvant CT regimens offered ($p<0.001$) (Table 5).

Table 3. 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 post-hoc analysis (a,b).

Table 4. Chemotherapy cycles offered before surgery according to groups

Offered cycles	Medical oncologists	Radiation oncologists	Surgeons
0	0 (a)	22 (b)	18 (b)
1	47 (a)	0 (b)	3 (a, b)
2	20 (a)	8 (a)	2 (a)
3	63 (a)	2 (b)	6 (a, b)
4 or more	54 (a)	4 (a)	6 (a)
Total	184	36	35

* Different letter shows statistical significance between groups in post-hoc analysis (a,b).

Table 5. Chemotherapy regimens offered 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 (a,b), 5-FU: 5-Fluorouracil; XELOX: Oxaliplatin plus Capecitabine; Folfox: Oxaliplatin, Leucovorin, 5-Fluorouracil.

Discussion

Similarities and differences in neoadjuvant treatment of rectal cancer by radiotherapists, medical oncologists, and surgeons, were evaluated. The ultimate goal of neoadjuvant treatment is CR, which can be achieved by 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. Indeed, pCR rates were demonstrated to be between 15-27% after neoadjuvant CRT and delayed surgery. [21] Although pCR is considered to be a good prognostic factor, 5-year OS is still the main determinant in this patient group.[22] Furthermore, Valentini et al showed 2 years DFS to be a better prognostic factor than pCR.[23] As such, the clinic utility of pCR is still controversial and needs to be further investigated. In contrast to other studies, our study population was formed of high numbers of CR patients. This has allowed for a valuable source of information in this patient group to be established, which may be valuable for future meta-analysis.

Response to CRT may be related to delays in carrying out surgery, [24] with the first strong study showing that six weeks of delay until surgery increased pCR in patients when compared to two weeks.[25] In another large study, 10-11 weeks of delay until surgery after neoadjuvant CRT had the highest pCR rates, though no increased response

rates were observed with waiting beyond this time interval.[26] Furthermore, retrospective data indicated that prolonging the interval between CRT and surgery increased CR rates, with Moore et al and Tulchinsky et al. demonstrating that waiting more than seven weeks increased CR rates significantly. [24,27] Another study confirmed this, and showed that an eight week waiting period doubled CR rates. [28] This data was strengthened further following a meta-analysis in 2005, which showed better outcomes and CR rates without significant morbidity. [29] However, waiting longer than 11 weeks did not result in a favorable outcome, as comparing a 7 week to an 11 week interval between CRT and surgery failed to show increased CR rates.[30] Similar to our results, there was no difference between a 4 and 8 week waiting period between CRT and surgery in a Turkish population study.[31] In our study, most of the participants considered the 7-8th and 11-12th weeks to be the optimal period for surgery. Meanwhile, a very small subset of the study population declared that they prefer to perform surgery after more than 13 weeks. Although a longer waiting period to surgery has been shown to increase CR rates, the optimal duration of the interval has yet to be firmly established.

Effects of genetic and racial differences on tumor response is not known, though data from Saglam et al. suggests that race had an impact on tumor response in the Turkish population.[31] Our findings were substantially similar to the findings from research conducted among Canadian surgeons in terms of optimal surgery time.[16] A higher rate of surgery before six weeks was found in this trial, which might be related to short-course radiation treatment without CT, and there was no difference between surgeons, oncologists, and radiotherapists. Another scenario-based questionnaire study did find a difference between optimal time of surgery decisions among surgeons, gastrointestinal oncologists, and radiotherapists. However, this study was focused on only the 6th and 8th weeks after CRT. [32]

The second controversial area is the addition of neoadjuvant CT to the treatment plan, whilst the optimal protocol and number of cycles remain under question. Garcia-Aguelar showed that adding two cycles of CT, including 5-FU, oxaliplatin, and leucovorin, increased pCR rates to 38%. In our study, more than 20% of patients received neoadjuvant CT, though there was no effect on prognosis in terms of OS. Also, the CT protocols and cycles were not eligible.[33] Preference for neoadjuvant CT was significantly higher amongst medical oncologists than in surgeons and radiotherapists. In a study by Lefevre et al., long-term CRT was preferred in the absence of contraindications, although there were differences between the groups analyzed. Indeed, the addition of neoadjuvant CT was not a frequent option for the 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 was the most preferred option amongst colorectal surgeons. However, there were differences between the colorectal surgeons in their study when compared to the surgeons in the current study. [17]

Selection of treatment strategy is largely 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. Indeed, treatment of low-risk patients with short-course RT and conventional long-course RT with concurrent CT yielded similar results.[34] However, recent published data demonstrated that conventional treatment had similar results to short-course RT followed by pre-operative oxaliplatin and CT, if the post-operative margin was at risk.[35] Differences between medical oncologists and other groups may depend on concerns of recurrence in particular groups, with a study investigating treatment preferences of radiation oncologists showing that most still prefer long-course RT. Meanwhile, Short-course RT was mainly preferred for patients who were not candidates for CT or where there were social barriers to long-course treatment. [36]

The 'Watch & Wait' strategy was less frequently selected in our study group (17%). In a study published by Crawford et al., 4.6 percent of participants selected the 'Watch & Wait' strategy, with 54.6% stating that they chose their strategy on a case by case basis and 40.9% favoring surgery.[16] Another study, investigating radiation oncologists, demonstrated that the 'Watch & Wait' strategy was preferred by 46%, which correlated with the OnCoRe trial. [37]

Limitations

The study was a survey that attempted to evaluate pitfalls in routine practice and hybrid treatment methods, but was unable to reveal many aspects of daily practice. Indeed, many particular situations such as total neoadjuvant treatment, CRM positivity, or utility of neoadjuvant CT regimens such as FOLFOXIRI were not fully explored. Furthermore, it was difficult to draw comparisons between groups as fewer radiotherapists and surgeons participated in the survey than medical oncologists. Also, high numbers of younger participants in the medical oncology group may have affected the results. This phenomenon was a result of an increased quota of

medical oncologists compared to surgical and radiation oncologists. Although there were significant difference in terms of experience, due to the longer education period for medical oncology in Turkey, this phenomenon may not have affected the results. Additionally, limited data in the literature comparing medical oncologists, radiation oncologists, and surgeons, made comparison with other studies difficult.

Conclusions

We found that the new pre-operative CT regimen with short-course RT has been slowly adopted into current practice. Also, medical oncologists tended to implement pre-operative CT more often when compared with the other groups. Optimal surgery time for patients receiving neoadjuvant treatment remains controversial.

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