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Impact of Professional Seniority on Total Neoadjuvant Treatment Approach for Locally Advanced Rectal Cancer

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ABSTRACT Objective: Total neoadjuvant therapy (TNT) integrates whole planned systemic chemotherapy within standard neoadjuvant protocols either before or after radiotherapy for locally advanced rectal cancer (LARC). However, the preference for neoadjuvant treatment type may vary among medical oncologists. We aimed to evaluate the impact of professional seniority on the TNT approach for LARC. **Material and Methods:** We presented a 20-item questionnaire to medical oncologists as a cross-sectional survey. The evaluation was stratified based on position: early-career oncologists (ECOs) and seniors. **Results:** We included 189 (62.4% ECOs) medical oncologists. Seniors significantly preferred using endorectal ultrasound as a staging tool (p=0.039). 65.6% of the participants preferred long-course chemoradiation. The most common denominators for TNT were external sphincter invasion, threatened circumferential resection margin (CRM), and clinical stage. ECOs and seniors preferred short-course radiotherapy (p=0.009) and long-course chemoradiotherapy (p=0.041), respectively, as the index step of TNT. Furthermore, 57% of the physicians preferred to monitor treatment response for TNT at 8-week periods. Approximately 47.1% of the participants reported pathological complete response (pCR) rates between 25% and 50% with TNT. The physicians who prefer to administer adjuvant treatment after TNT completion make individualized decisions when surgical pathology reveals non-pCR, CRM, and lymph node involvement. Furthermore, 88% of the senior medical oncologists and 76.3% of the ECOs agreed that TNT should be the standardized neoadjuvant treatment approach for LARC. **Conclusion:** TNT for LARC is well accepted among medical oncologists, and professional seniority seems to affect its clinical application.

Keywords: Total neoadjuvant therapy; rectal cancer; oncologists; senior

Total neoadjuvant therapy (TNT) integrates planned systemic chemotherapy (ChT) before or after radiotherapy (RT) for locally advanced rectal cancer (LARC).[1] Increased compliance with planned oncological therapy, tumor down-staging, ChT administration at the earliest stage, and evaluating tumor chemosensitivity are the proposed benefits of TNT. Because randomized trials evaluating proper TNT sequence and practice are limited, physicians hesitate to implement this strategy.[2,3] Although TNT has been used in different forms in the last decade, it has been recently offered as one of the treatment approaches for LARC.[4] The optimal sequence for ChT or RT and the type of systemic treatment and RT are not clarified in the guidelines.[5]

The patient selection criteria for TNT use in rectal cancer are unclear.[6] Moreover, decision-making in oncology requires a plethora of different criteria. Generally, only 6% of the National Comprehensive Cancer Network (NCCN) recommendations were based on high-level evidence. Sometimes, lower levels of evidence or expert opinions were used to select the best treatment option.[4]

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The oncologists' experience can be a factor in the use of TNT in clinical settings. This survey study among medical oncologists aimed to evaluate how professional seniority affects the TNT administration for LARC.

MATERIAL AND METHOD

This study was conducted as a cross-sectional survey among medical oncologists (Appendix 1). We prepared a 20-item questionnaire that was presented to medical oncologists during a national oncology congress via tablets. The questions were distributed as follows: 2 for work experience regarding rectal cancer treatment, 5 for physicians' choice in terms of screening and treatment in rectal cancer and factors affecting their choices, and 13 for the TNT approach (sequencing, denominators of sequencing, ChT preference, treatment response evaluation, operation choice, adjuvant treatment denominators). More than one answer was applied to 10 treatment-related questions. The survey questions are seen in the supplement file.

The questionnaire evaluation was stratified based on position: early-career oncologists (ECOs), defined as within 5 years after completing medical oncology training, and seniors.[7] It was also stratified based on the caseload of physicians annually: high-volume medical oncologists were defined as treating >20 patients with rectal cancer annually.

The Acıbadem University Ethics Committee approved this study on December 3, 2021 (no:2021/23). Furthermore, the study was conducted following the Declaration of Helsinki. Data obtained were entered into the IBM SPSS Statistics 21.0 USA, program, and frequency analysis was performed. Additionally, chi-square tests were used to compare nominal variables. Statistical significance was determined using $p<0.05$.

RESULTS

This study included 189 medical oncologists, of which 108 and 81 were men and women, respectively. Annually, 32%, 31.2%, and 24.9% of physicians treat 6-20, 21-50, and >50 patients with rectal cancer, respectively. The most preferred imaging modality used for staging were positron emission computed tomography (PET-CT) and magnetic resonance imaging (MRI). The use of endorectal ultrasound (ERUS) was significantly higher among senior medical oncologists (33.8% vs 20.3%, p=0.039).

Long-course chemoradiation and TNT were used by 65.6% and 50% of the participants and physicians in daily practice, respectively. Regardless of professional seniority, the preference for neoadjuvant treatment was similar among the participants (p=0.925). The most common denominators for TNT preference over traditional neoadjuvant treatment alternatives were external sphincter invasion, threatened circumferential resection margin (CRM), and clinical stage (Table 1). The denominators of TNT preference were not significantly different between ECOs and senior physicians. However, the main denominators for TNT preference were external sphincter invasion and positive CRM among the high-volume medical oncologists (p=0.005). The most preferred TNT sequence was RT first approach (66.6%). Although ECOs preferred short-course RT as the index step of TNT (p=0.009), the seniors preferred the long-course chemoradiotherapy first approach (p=0.041). The preferred ChT regimen for TNT was capecitabine-oxaliplatin (CAPEOX) in 63% of the participants, followed by 5-fluorouracil/LV and oxaliplatin (FOLFOX) (53.9%). The denominators of the ChT type for TNT were age/comorbidities (81.8%) and stage (56%) (Table 1).

57% of the physicians preferred to monitor treatment response for TNT at 8-weeks periods (p=0.035, Table 2). The most preferred time for re-staging and time for surgery after completion of TNT was 5-6 and 7-8 weeks (38.6% and 53.3%, respectively). Moreover, 43% of the participants agreed that TNT or neoadjuvant treatment changes operative strategy. Additionally, 47.1% of the participants reported pathological complete response (pCR) rates between 25% and 50%. The physicians (59.8%) who prefer to administer adjuvant treatment after TNT completion make individualized decisions. The parameters for administering adjuvant ChT were positive CRM (56.6%), lymph node metastases (55.5%), and non-pCR (57.6%). However, the choice for adjuvant ChT based on CRM positivity was significantly different between the ECOs and seniors (63.6% vs. 45.1%,

APPENDIX 1: Neoadjuvant treatment in locally advanced rectal cancer.

1. Experience in rectal cancer treatment
- a. 1-5 years
- b. 6-9 years
- c. 10-19 years
- d. >20 years

2. Annual volume of rectal cancer treatment
- a. 1-5
- b. 6-20
- c. 21-50
- d. >50

For questions, 3-11, check all that apply.

3. Imaging modalities for staging
- a. MRI
- b. ERUS
- c. CT
- d. PET
- e. Other

4. Type of neoadjuvant treatment preference
- a. ChT
- b. RT
- c. Long-course (ChT+RT)
- d. Total neoadjuvant treatment

5. Denominators of TNT preference over conventional neoadjuvant treatment
- a. Age/comorbidities
- b. Tumor location
- c. Stage
- d. Clinical symptoms (tenesmus/bleeding/pain)
- e. External anal sphincter invasion/CRM positivity

6. Denominators of conventional neoadjuvant treatment over RT
- a. Age/comorbidities
- b. Tumor location
- c. Stage
- d. Clinical symptoms (tenesmus/bleeding/pain)
- e. External anal sphincter invasion/CRM positivity

7. Denominators of RT only
- a. Age/comorbidities
- b. ECOG/Karnofsky performance scale
- c. Risk of COVID infection
- d. Tumor location
- e. Stage

8. Primary TNT sequencing preference
- a. ChT --> long-course (ChT+RT) --> surgery
- b. ChT --> short-course RT --> surgery
- c. Long-course (ChT+RT) --> ChT --> surgery
- d. Short-course RT --> ChT --> surgery

9. Denominators of TNT sequencing (check all that apply)
- a. Age/comorbidities
- b. Tumor location
- c. Stage
- d. Clinical symptoms (tenesmus/bleeding/pain)
- e. External anal sphincter invasion/CRM positivity

APPENDIX 1: Neoadjuvant treatment in locally advanced rectal cancer *(continue)*.

10. Preferred ChT regimen for TNT
- a. CAPEOX
- b. FOLFOX
- c. FOLFIRINOX

11. Denominators of preferred ChT regimen for TNT
- a. Age/comorbidities
- b. Tumor location
- c. Stage
- d. Clinical symptoms (tenesmus/bleeding/pain)
- e. External anal sphincter invasion/CRM positivity

12. Time to treatment response evaluation
- a. 8 w
- b. 12 w
- c. 16 w

13. Time to re-staging after completion of TNT
- a. 2-4 w
- b. 5-6 w
- c. >6 w

14. Time to surgery after completion of TNT
- a. 2-4 w
- b. 5-6 w
- c. 6-8 w
- d. >9 w

15. TNT/neoadjuvant treatment changes operative strategy
- a. Strongly agree
- b. Agree
- c. Neither agree nor disagree
- d. Disagree
- e. Strongly disagree

16. Your pCR rate after TNT
- a. 0%-25%
- b. 25%-50%
- c. 50%-75%
- d. 75%-100%

17. Adjuvant treatment after TNT
- a. Yes
- b. No

18. If yes, the rationale behind the adjuvant treatment after TNT (check all that apply)
- a. Positive surgical margin
- b. ypN+
- c. Non-pCR
- d. High-risk features at the time of diagnosis (cT4/cN+/CRM)

19. If yes, adjuvant regimen after TNT (check all that apply)
- a. Capecitabine
- b. Infusional 5-FU
- c. FOLFOX
- d. CAPEOX

20. TNT should be the standard neoadjuvant approach for locally advanced rectal cancer
- a. Strongly agree
- b. Agree
- c. Neither agree nor disagree
- d. Disagree
- e. Strongly disagree

TABLE 1: Denominators of TNT for locally advanced rectal cancer.

	ECOs n=118(%)	Senior n=71(%)	p value
Determinants of TNT preference over conventional neoadjuvant therapy			
Age/co-morbidity	55 (46.6)	26 (36.6)	0.179
Tumor location	49 (41.5)	35 (49.3)	0.298
Stage	76 (64.4)	42 (59.2)	0.470
Symptoms	36 (30.5)	25 (35.2)	0.503
External sphincter invasion/positive CRM	62 (52.5)	37 (52.1)	0.954
TNT preference			
ChT ->long-course (ChT+RT) ->surgery	39 (33.1)	17 (23.9)	0.184
Cht ->short-course RT ->surgery	22 (18.6)	15 (21.1)	0.677
Long-course (ChT+RT) ->ChT ->surgery	55 (46.6)	44 (61.9)	0.041
Short-course RT -> ChT -> Surgery	23 (19.5)	4 (5.6)	0.009*
Determinants of TNT preference			
Age/co-morbidity	74 (62.7)	42 (59.2)	0.627
Tumor location	64 (54.2)	44 (61.9)	0.298
Stage	74 (62.7)	45 (63.3)	0.927
Symptoms	63 (53.4)	35 (49.3)	0.585
External sphincter invasion/positive CRM	54 (45.8)	38 (53.5)	0.301
Preferred ChT regimen for TNT			
CAPEOX	74 (62.7)	46 (64.8)	0.774
FOLFOX	62 (52.5)	40 (56.3)	0.612
FOLFIRINOX	20 (16.9)	13 (18.3)	0.811
Determinants of preferred ChT regimen for TNT			
Age/co-morbidity	94 (79.7)	60 (84.5)	0.406
Tumor location	39 (33.1)	28 (39.4)	0.374
Stage	68 (57.6)	38 (32.2)	0.582
Symptoms	31 (26.3)	24 (33.8)	0.270
External sphincter invasion/positive CRM	33 (27.9)	15 (21.1)	0.296

*Fisher's exact test; ECO: Early-career oncologist; TNT: Total neoadjuvant therapy; CRM: Circumferential resection margin; ChT: Chemotherapy; RT: Radiotherapy; CAPEOX: Capecitabine-oxaliplatin; FOLFOX: 5-fluouracil/LV and Oxaliplatin; FOLFIRINOX: 5-fluouracil-leucovorin-irinotecan-oxaliplatin.

p=0.013). CAPEOX (51.1%) and capecitabine alone (46%) were the preferred adjuvant ChT after TNT. The ChT protocol preference was not significantly different between ECOs and senior physicians (p=0.959 and 0.158, respectively). The majority of the senior medical oncologists (88%) and ECOs (76.3%) agreed that TNT should be the standardized neoadjuvant treatment approach for LARC.

DISCUSSION

Studies showed that TNT as a treatment option for LARC resulted in high pCR rates and tolerance of therapy with neoadjuvant ChT and chemoradiation preoperatively.[8-10] This study showed that TNT for LARC is well accepted among medical oncologists, and professional seniority affects its clinical application. Although the European Society for Medical Oncology follows the conventional neoadjuvant options, the NCCN guidelines recommend TNT as one of the new standardized treatments in selected patients.[11] However, long-term follow-up is needed to determine whether TNT can improve survival or further ease nonoperative strategies. TNT approach requires close follow-up and experienced multidisciplinary teamwork, which makes it difficult to use in daily practice.

The NCCN guidelines recommend chest and abdominal CT and pelvic MRI for staging rectal cancer after diagnosis.[12] ERUS is recommended if MRI is contraindicated, inconclusive, or for superficial lesions, whereas pre-operative staging PET-CT scan is not advised routinely. Studies showed that combin-

TABLE 2: Follow-up characteristics of TNT for locally advanced rectal cancer.

	ECOs n=118 (%)	Senior n=71 (%)	p value
Evaluation of treatment response after TNT (w)			
8	62 (52.5)	46 (64.8)	0035*
12	56 (47.5)	25 (33)	
Time to restaging after completion of TNT (w)			
2-4	34 (28.8)	16 (22.5)	0.638
5-6	44 (37.3)	29 (40.8)	
>6	40 (33.9)	26 (36.6)	
Time to operation after completion of TNT (w)			
2-4	26 (22.1)	11 (15.5)	0.085
5-6	23 (19.5)	6 (8.5)	
7-8	57 (48.3)	44 (61.9)	
≥9	12 (10.2)	10 (14.1)	
pCR rate after TNT (%)			
0-25	21 (17.8)	22 (30.1)	0.062*
26-50	56 (47.5)	33 (46.5)	
51-75	38 (32.2)	13 (18.1)	
76-100	3 (2.5)	3 (4.2)	
Adjuvant therapy after TNT			
Yes	23 (19.5)	13 (18.3)	0.932
No	24 (20.3)	16 (22.5)	
Patient-based decision	71 (60.2)	42 (59.2)	
If yes, reason for adjuvant therapy after TNT			
Positive CRM	75 (63.6)	32 (45.1)	0.013
ypN+	66 (55.9)	39 (54.9)	0.893
Non-pCR	70 (59.3)	39 (54.9)	0.554
High risk factors at the time of diagnosis (cT4/cN+/CRM+)	61 (51.7)	32 (45.1)	0.378
If yes, choice of adjuvant treatment regimen after TNT			
Capecitabine	59 (50)	28 (39.4)	0.158
Infusional 5-FU	13 (11.1)	9 (12.7)	0.731
FOLFOX	39 (33.1)	33 (46.5)	0.066
CAPEOX	61 (51.7)	37 (52.1)	0.959
TNT should be the standard neoadjuvant approach in LARC			
Agree	90 (76.3)	63 (88.7)	0.089*
Neutral	23 (19.5)	6 (8.5)	
Disagree	5 (4.2)	2 (2.8)	

*Fisher's exact test; ECO: Early-career oncologist; TNT: Total neoadjuvant therapy; CRM:Circumferential resection margin; w: Weeks; N: Lymph node; pCR: Pathological complete response; CAPEOX: Capecitabine-oxaliplatin; FOLFOX: 5-fluouracil/LV and Oxaliplatin; LARC: Locally advanced rectal cancer.

ing ERUS with MRI may increase the sensitivity and specificity of staging.[13] The most popular imaging modalities in our study population were PET-CT and MRI. ERUS, preferred mostly by seniors, may not be a readily available staging modality for the ECOs who frequently work in state hospitals or rural areas. PET-CT affects clinical management by guiding biopsy or surgery and may change therapy options.[14] Its use in daily practice, especially if easily accessible, makes physicians more confident.

Studies comparing TNT with standard neoadjuvant treatment modalities showed promising preliminary data, making most physicians implement this approach in their daily practice.[15] Our survey showed that long-term chemoradiotherapy is the leading treatment option. This may be due to the heterogeneous results of TNT studies that pose challenges in generalizing its clinical use. Strong candidates for the TNT approach are patients with low T3 tumors with an involved CRM, T4 tumors, or N1/2 dis-

ease.[12] Our study showed that medical oncologists, regardless of their professional experience, preferred TNT over the traditional neoadjuvant approach depending on the advanced stage and external sphincter invasion.

Although early studies reported the superiority of TNT over the standard approach, issues regarding the optimal sequencing of treatment (ChT first or RT first approach) are unresolved. Ozer et al. proposed a patient-tailored algorithm that can guide physicians in routine practice.[6] The decision to choose an approach is based on the physicians' attitude, patient characteristics, and familiarity. Our results showed a statistically significant difference between seniors and ECOs in terms of the type of RT within TNT. Moreover, senior physicians seem more dedicated to traditional methods and prefer long-course chemoradiotherapy as their first line while sequencing TNT. In patients with a high risk for distant metastases, long-course chemoradiotherapy may be a good choice in terms of earlier control.[12] However, ECOs used short-course RT first approach in daily practice, which may be due to rapid relief of symptoms, requirement of an abdominoperineal resection, poor physical performance status, and presence of tenesmus and intractable rectal bleeding.[6] ECOs may prefer a short-term RT first approach in the light of Rectal Cancer and Pre-operative Induction Therapy Followed by Dedicated Operation trial (RAPIDO) results, whereas seniors prefer a conventional neoadjuvant treatment approach, long-course chemoradiotherapy first approach.[3]

TNT treatment approach promoted the nonoperative watch-and-wait strategy that Habr-Gama et al. introduced in 1998.[16] Different retrospective studies supported the high survival rates (97.7% and 84% for overall and disease-free survival, respectively), leading to the adoption of the strategy in daily practice in patients with complete clinical response.[17,18] The physicians who agreed that TNT changes operative strategy (43%) might be using the watch-and-wait approach for appropriate patients.

CAPEOX and FOLFOX were the most preferred treatment protocols during ChT, and the decision was based on the age and comorbidities of patients. CAPEOX was more suitable for patients who prefer to have a short hospital stay, especially in elderly patients. Particularly, this is currently used considering the coronavirus 2019 (coronavirus disease-2019) pandemic. Furthermore, the preference may be due to the absence of an infusion port. In most trials, TNT studies using FOLFOX and 5-fluorouracil-leucovorin-irinotecan-oxaliplatin (FOLFIRINOX) as ChT protocol included patients with ECOG performance status of 0, and the median age in either trial was 61 years.[1,19] FOLFIRINOX is rarely preferred by physicians, although it is the protocol used in the PRODIGE 23 trial, one of the studies causing TNT to be the new standard of care.[1] The decreased use of FOLFIRINOX may be due to the decreased tolerance to treatment. The PRODIGE 23 trial showed that 92% of patients completed neoadjuvant courses; however, only 79% received adjuvant ChT, and only 81% of these could complete all 6 cycles. Long-term exposure to oxaliplatin may result in overtreatment and unnecessary toxicity. Although FOLFIRINOX is recommended, especially for T4 tumors with positive lymph nodes, it is rarely used in clinical practice.

Our survey results showed that the physicians assessed treatment response every 8 weeks. If no response is seen after 2 months, directly moving to chemoradiotherapy is recommended.[20] The most preferred time for surgery after treatment completion was 7-8 weeks for most medical oncologists, which was also the recommended time in the guidelines.[12] The high pCR rates with the TNT approach may be due to the increasing interval between RT and surgery. The reported pCR rates were 25-50% with TNT among the participants. Two studies reported that the pCR rates with TNT were 28% and 36%.[19,21]

Adjuvant treatment is not recommended for patients who completed planned TNT.[12] However, physicians chose a patient-based approach to decide on adjuvant treatment based on the surgical pathology results. Non-pCR is a reasonable denominator of adjuvant ChT because recurrence rates are higher among these patients. Extending the treatment period makes physicians more confident in terms of disease

recurrence. Another leading parameter for using adjuvant treatment is CRM positivity, especially among the ECOs. Phase 2 studies investigating the implementation of immunotherapy (pembrolizumab or durvalumab) in a neoadjuvant setting are ongoing, regardless of microsatellite status.[22,23] The role of immunotherapy in TNT will be clear after the results. Other than immunotherapy, the adjuvant ChT approach in patients with non-pCR after TNT is controversial.

Our study has some limitations. The survey was conducted in a small study population consisting of medical oncologists only, and radiation oncologists or general surgery physicians could contribute with different perspectives. More questions might have helped to obtain a more detailed analysis of physicians' approaches. By contrast, rapid data collection and collection of full response rates were the strengths of our study.

CONCLUSION

Regardless of professional experience, most of medical oncologists preferred TNT as the standardized treatment approach for LARC. The main expectation is increasing the pCR rates, which can potentially lead to new approaches more frequently offered, such as the watch-and-wait approach. Long-term follow-up will clarify if the high pCR rates will result in improved survival and cause junior physicians to feel safer about TNT. The eagerness to use TNT to achieve increased pCR rates may cause overtreatment in a considerable number of patients.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Erman Aytaç, Leyla Özer, İbrahim Yıldız;* ***Design:*** *Elif Şenocak Taşçı;* ***Control/Supervision:*** *Erman Aytaç, Leyla Özer, İbrahim Yıldız;* ***Data Collection and/or Processing:*** *Elif Şenocak Taşçı, Miraç Ajredini, Arda Ulaş Mutlu;* ***Analysis and/or Interpretation:*** *Arda Ulaş Mutlu, Erman Aytaç, Leyla Özer, İbrahim Yıldız, Elif Şeocak Taşçı;* ***Literature Review:*** *Elif Şenocak Taşçı;* ***Writing the Article:*** *Elif Şenocak Taşçı;* ***Critical Review:*** *Erman Aytaç, Leyla Özer, İbrahim Yıldız, Elif Şeocak Taşçı;* ***References and Fundings:*** *Elif Şenocak Taşçı;* ***Materials:*** *Elif Şenocak Taşçı.*

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