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Research Article

Does Waiting Time from Diagnosis to Treatment Affect Outcome in Locally Advanced Rectal Cancer? Real World Data Analysis

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ABSTRACT

Introduction: Rectal cancer is a common and lethal disease, with approximately 44,180 new cases of diagnosed annually in the United States and a five-year survival of 67% [1, 2]. The interval from diagnosis to chemoradiation treatment, or waiting time (WT), is considered to be an important quality indicator for cancer care and has been demonstrated to be associated with oncologic outcomes in various cancers [3, 4]. The current recommendation for pre-treatment staging evaluation includes rigid proctoscopy, PET CT, transrectal ultrasound (TRUS) and often rectal MRI. These diagnostic procedures may significantly postpone the start of treatment. We aim to examine the effect of WT on overall survival (OS) and disease free survival (DFS) of rectal cancer patients.

Methods: Retrospective analysis was performed in a detailed database of patients with resectable primary rectal cancer who underwent chemoradiation between January 2000 and January 2019. Univariate and multivariate cox proportional hazard regressions were conducted in order to evaluate the effect of WT on oncological outcomes.

Results: 387 patients were enrolled in our database; of them 297 patients were eligible by the inclusion criteria. Median WT was 6.3 weeks (IQR 4.3-8.7). Multivariate analysis showed adjusted Hazard Ratio (HR) for OS increases by 1.07 for each additional week of therapeutic delay in all age groups ($p=0.025$). Furthermore, focusing on the majority of patients in the age group 45 - 70 years, adjusted HR for OS increases by 1.12 for each additional week of therapeutic delay ($p=0.011$). Adjusted HR for DFS increases by 1.06 for each additional week of therapeutic delay in all age groups ($p=0.045$) and an increment by 1.09 for each additional week of therapeutic delay in age group 45-70 years ($p=0.02$).

Conclusion: Prolonged WT leads to significant poorer overall survival in patients with primary rectal cancer who underwent chemoradiation and curative surgical treatment. This marks the importance of efficient diagnostic evaluation and clinical multidisciplinary decision making in a timeframe of 6 weeks in order to not jeopardize oncological outcomes.

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Background

Rectal cancer is a common and lethal disease, with approximately 44,180 new cases diagnosed annually in the United State and a five-year survival of 67% [1, 2]. According to current guidelines, the recommended treatment for stage III rectal cancer includes long-term

neoadjuvant chemotherapy and radiation therapy (hereafter, chemoradiotherapy) followed by surgery. Diagnostic procedure recommended prior to the initiation of CRT include trans-rectal US and pelvic MRI, aiming at local assessment of the tumor and FDG-PET CT aiming at the assessment of metastatic spread [6]. Adverse effects of delaying radiation treatment on survival is well known in various malignancies, including small cell lung cancer and breast cancer [8, 9].

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Over the past three decades, the association between WT and mortality has been the subject of several studies based on data from symptomatic colon and/or rectal cancer patients [10, 12, 13, 15, 16]. The studies report either no statistically significant association or the waiting time paradox (findings of higher mortality for short delays was caused by hidden confounders like the tumor's speed of growth and/or its ability to spread) [17, 20]. According to this theory, aggressive tumors are associated with shorter delays because they are easier to appraise [3]. Most of the studies focus on diagnostic intervals from symptoms to biopsy rather than WT from biopsy to initiation of chemoradiation. A recent study found that prolonged treatment delay does not lead to poorer overall or cancer-free survival in patients with primary colorectal cancer who underwent curative surgical treatment [21].

In Israel, all required diagnostic procedures are accessible and universally reimbursed. Yet, their completion is often prolonged due to long waiting times, thus delaying the start of chemoradiotherapy. We report here on the association between time to treatment and survival in a consecutive population of stage III rectal cancer patients, treated at a single institution.

Patients and Methods

I Study Design

We performed a retrospective review of a prospectively entered database on 297 consecutive patients with biopsy-proven locally advanced (T3-4 or N1 and/or clinically bulky) low (at or below 5 cm from the anal verge) and mid- (6–11 cm from the anal verge) rectal adenocarcinoma who underwent neoadjuvant therapy followed by radical resection with total

mesorectal excision (TME) for curative intent between October 2000 and December 2019.

The examined parameters included date of diagnosis, beginning of radiation therapy, clinical staging, final pathology, imaging modalities, radiation dose and survival data. The pre-treatment staging was based on rigid rectoscopy for localization of the tumor in the rectum, endorectal ultrasonography (EUS), and computerized tomography (CT) of the pelvis for local tumor status, abdominal CT, chest X-ray, and/or chest CT to rule out distant metastases. The neoadjuvant regimen included high-dose radiation therapy of 45–50.4 Gy, usually with concomitant 5-fluorouracil (FU)-based chemotherapy. Radiotherapy was administered 5 days per week for 5.5 weeks. Patients were treated with 5-FU either in continuous infusion (180 mg/m² / day) for 5 days per week during 5 weeks or as oral preparations. Surgery was planned 6–8 weeks following the completion of preoperative therapy but was changed according to bed availability on the surgical ward.

Routine postoperative follow-up of patients included physical examination and serum carcinoembryonic antigen every 3–4 months in the first 2 years after surgery and then every 6 months. Colonoscopy was performed a year after surgery and if normal every 3 years thereafter. CT of the chest, abdomen, and pelvis was done yearly in the first 2 years of follow-up. Survival was considered the interval between surgery and last follow-up or death (OS) or the date of last follow-up or recurrence (DFS). Patterns of disease recurrence (local and/or distant), DFS, and OS were analyzed. Waiting time was defined from day of biopsy to initiation of chemorad (Figure 1). The institutional Helsinki Committee approved this study.

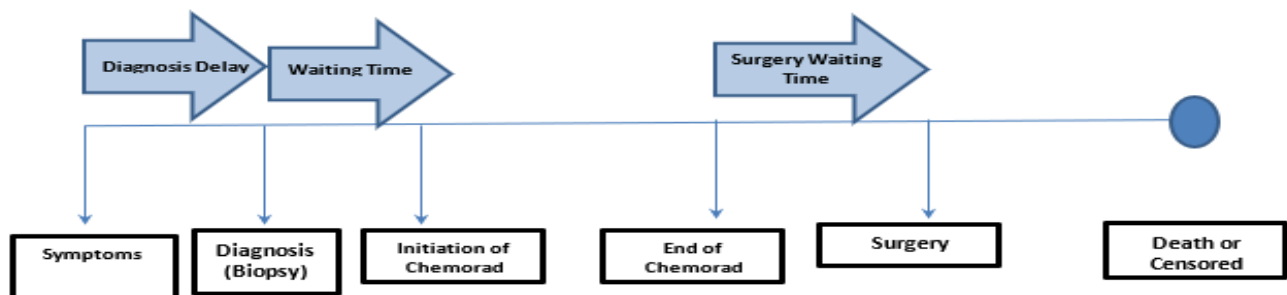


Figure 1: Study timeline and variables.

II Statistical Analysis

Data was analyzed using descriptive statistics. OS and DFS were calculated using Kaplan-Meier estimators. P-values for difference in the survival curves were determined using the log-rank test. Univariate and multivariate cox proportional hazards were conducted in order to evaluate the effect of WT on oncological outcomes. For all analyses, two-sided p-values of less than 0.05 were considered statistically significant.

Results

The institutional database included 297 patients with locally advanced rectal cancer who met the inclusion criteria of the study. Their median age was 63, 114 were females, 183 were males. 66% of patients

population presented at age 45–70 years. 8% were young adults 45 years and younger, 26.3% were elderly above 70 years. (Table 1). All patients completed rigid proctoscopy, 89% completed TRUS and 62% completed a PET-CT. Most patients had positive lymph nodes on imaging studies (68%). Only 3% of patients had T2NO disease, 24% had T3NO, and 0.7% had T4NO. The median WT was 6.3 weeks (range, 4.3–8.7 weeks) (Figure 2). All patients completed radiation therapy; of those, 95.9% of patients received 5-FU/Xeloda. Median waiting time from the end of chemoradiation to surgery was 8.6 weeks (range 7–11.3 weeks). Most patients (71%) underwent low anterior resection (LAR) and the rest underwent abdominal perineal resection (APR). TME was conducted in 68% of the patients. Pathologic disease stage was complete response (20%), stage I (30%), stage II (24%), stage III (25%). 241 patients (88%) received adjuvant chemotherapy (Table 2).

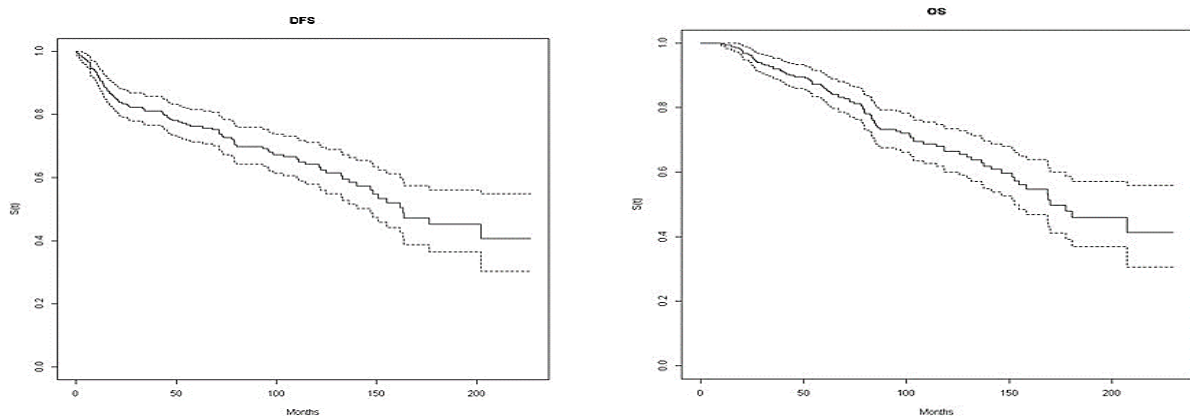


Figure 2: Disease free survival and overall survival in patients population.

Overall description of the patients population median DFS and OS. Dashed line stands for confidence interval.

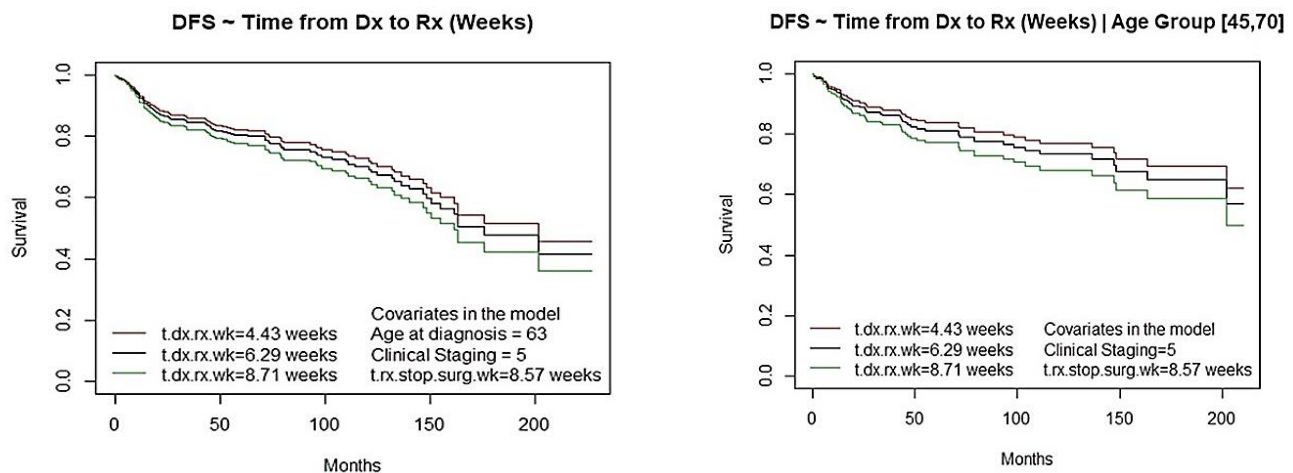


Figure 3: WT effect on DFS using multivariate predictive model.

Predicted DFS from the relevant multivariate Cox-PH model is provided. The co-variables adjusted included: age at diagnosis, clinical stage and surgery waiting time (from end of radiotherapy to surgery date). Each graph in the figure represent different model values: in red Q1 of the WT (4.43 weeks), in purple Q2 (median) of the WT (6.29 weeks) and in green Q3 of the WT (8.71 weeks). As the WT increases, the DFS worsens, in accordance with adjusted HR 1.06 in all age groups ($p=0.045$) **A** and HR 1.09 in age group 45-70 years ($p=0.02$) **B**.

Survival

At a median follow up of 115 months 7.4% of patient population experienced local recurrence and 29.6% deceased. Median DFS and OS were 163 and 170 months, respectively (Figure 3). WT effect on DFS and OS was evaluated using a univariate cox-model which showed a trend to significant HR 1.04 ($p=0.067$) for OS in age group 45-70. Therefore, a multivariate analysis was conducted and was adjusted to age, clinical stage and surgery waiting time. Adjusted HR for DFS was increased by 1.06 for each additional week of therapeutic delay in all age groups ($p=0.045$) and a significant increment by 1.09 for each additional week of therapeutic delay in age group 45-70 years ($p=0.02$) (Figure 4). The effect on overall survival, was also estimated by multivariate analysis adjusted to age, clinical stage and surgery waiting time. Adjusted HR for OS was increased by 1.07 for each additional week of therapeutic delay in all age groups ($p=0.025$) and an increment by 1.12

for each additional week of therapeutic delay in age group 45-70 years ($p=0.011$) (Figure 5).

Discussion

Our study indicates significant association between longer WT and reduced survival in stage III rectal cancer patients. Prolonged diagnostic WT can be attributed to multiple 'second opinions' and inappropriate referral to imaging tests. Potential outcomes of delay could include decreased patient satisfaction, increased patient worry, and inefficient or wasteful use of medical services if inappropriate tests are ordered. Moreover, treatment delay in rectal cancer patients is affected not only by clinicopathological factors, but also by sociocultural ones. Healthcare providers should pay greater attention to social groups with less formal education in order to optimize treatment attention [22].

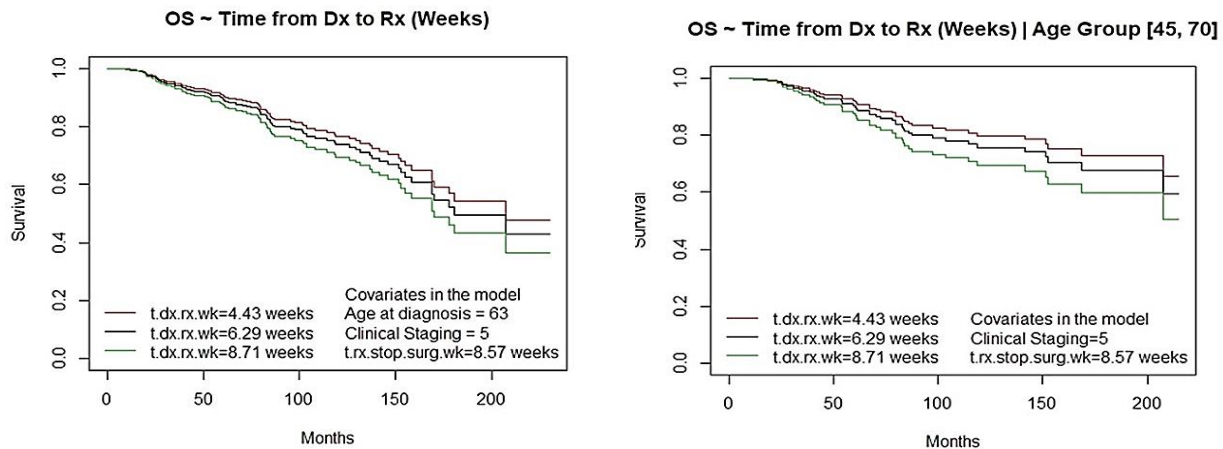


Figure 4: WT effect on OS using multivariate predictive model.

Predicted OS from the relevant multivariate Cox-PH model is provided. The co-variants adjusted included: age at diagnosis, clinical stage and surgery waiting time (from end of radiotherapy to surgery date). Each graph in the figure represent different model values: in red Q1 of the WT (4.43 weeks), in purple Q2 (median) of the WT (6.29 weeks) and in green Q3 of the WT (8.71 weeks). As the WT increases, the OS worsens, in accordance with adjusted HR 1.07 in all age groups ($p=0.025$) **A** and HR 1.12 in age group 45-70 years ($p=0.011$) **B**.

Table 1: Demographic and presenting clinical parameters of the study cohort.

<i>N</i>	297
<i>Gender</i>	
Female(%)	114 (38.4)
Male(%)	183 (61.6)
<i>Median years of age</i>	63
<i>Age at presentation (%)</i>	
>45	23 (7.7)
45-70	196 (66)
<70	78 (26.3)
<i>Completion of imaging studies (%)</i>	
Rigid proctoscopy	297 (100)
TRUS	258 (89)
PET CT	186 (62.8)
<i>Clinical Staging (%)</i>	
T2 NO (sphincter involvement)	9 (3.3)
T3 NO	65 (24)
T4 NO	2 (0.7)
Any T Positive Lymph Nodes	183 (67.5)
<i>Completion of Radiotherapy (%)</i>	297 (100)
<i>Completion of Xeloda/5fu (%)</i> (during radiotherapy)	282 (95.9)
<i>Surgical Procedure (%)</i>	
APR	82 (27.6)
LAR	212 (71.4)
OTHERS	3 (1)
<i>TME (%)</i>	
Complete	78 (68.4)
Incomplete	36 (31.6)

It is important to differentiate between diagnostic delays, treatment delays and surgery delays which are often discussed together. Diagnostic delays greater than 60 days has been shown to be significantly associated with more advanced stage at diagnosis [23]. On systematic review, 20 of 26 studies on Colorectal cancer (CRC) delays showed no association

between diagnostic or treatment delays and survival, and four studies actually showed that longer delay was associated with better prognosis [24]. In a companion meta-analysis, no statistically significant association was found between diagnostic and treatment delays and disease stage when considering colon and rectal cancers collectively. Analyzed separately, longer delays were associated with later stages for rectal cancer, but earlier stages for colon cancer [16, 25-27]. The above mixed findings in literature can be attributed in part to method limitations, including analyzing colon and rectal cancers together and having smaller cohort samples.

Table 2: Treatment outcomes: recurrences and survival data.

<i>Pathological staging (%)</i>	
0 (complete response)	56 (18.9)
1	91 (30.6)
2	70 (23.5)
3	79 (26.5)
<i>Tumor Grade (%)</i>	
Well differentiated	21 (11.9)
Moderate differentiated	113 (64.2)
Poorly differentiated	13 (7.4)
Mucinous	29 (16.5)
<i>Adjuvant chemotherapy (%)</i>	258 (86.9)
Yes	39 (13.1)
No	
<i>Local recurrence (%)</i>	
Yes	19 (7.4)
No	239 (92.6)
Missing data	39
<i>Death (any cause) (%)</i>	
Yes	88 (29.6)
no	209 (70.4)

Different health systems abroad have adopted timeliness guidelines. For example, according to UK guidelines, patients with suspected cancer should see a specialist within 2 weeks and treatment should begin within

a month of diagnosis [28]. The key strength of this study lies in the large number of cases reflecting real life data of Israeli patients diagnosed, treated and operated by the same team in a tertiary referral center. Contrary to previous studies, our patient population includes primary rectal cancer only. The present study carries a number of limitations that need to be considered for proper interpretation of the results. Perhaps the main limitation of this study is its retrospective design, which makes it vulnerable to information bias from inaccurate clinical records and missing data. Data regarding MRI evaluation was not collected. Other measured confounding variables such as comorbidities or emergency admission may also have influenced the results and were not recorded.

In conclusion, clinicians should complete diagnostic evaluation within scheduled timeframe up to 6 weeks. Our statistical model approves that each additional week of therapeutic delay significantly jeopardizes oncological outcomes and prognosis. Further prospective research on similar combined data sets from longitudinal studies should be conducted to confirm the relative impact of diagnostic intervals on outcomes in patients with rectal cancer.

Conflicts of Interest

None.

Financial Disclosure

None.

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