PROTOCOL TITLE

Evaluation of clinical outcome in Asian patients with localised rectal adenocarcinoma managed with watch-and-wait approach by developing a multinational collaborative database.

Short title: Asian Watch-and-Wait Database (AWWD)

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

cCR: Clinical Complete Response
DFS: Disease free survival
DICOM: Digital Imaging and Communications in Medicine
DSMB: Data safety and monitoring board
ECOG: Eastern Cooperative Oncology Group
EORTC: European Organisation for Research and Treatment of Cancer
IQR: Inter Quartile Range
OS: Overall Survival
PI: Principal Investigator
QLQ: Quality of Life Questionnaire
QOL: Quality of Life
REDCap: Research Electronic Data Capture
SD: Standard Deviation
SPSS: Statistical Package for the Social Sciences
TME: Total Mesorectal Excision
TNT: Total Neoadjuvant Therapy

SUMMARY

The standard treatment approach of localised rectal adenocarcinoma involves neoadjuvant radiotherapy and chemotherapy followed by assessment for surgery and optional adjuvant chemotherapy. However, such patients who achieve complete of near complete clinical response after neoadjuvant therapy are increasingly being managed with the 'Watch-and-Wait strategy' in the recent years. Although safety of such policy has been established, the patient population in the published studies are not represented well by Asian population. Moreover, the data about safety of such policy in the setting of modern neoadjuvant strategies is limited. We propose a multinational collaborative prospective database study in Asia to systematically collect data on patients being managed with such a strategy. The target population is patients with localised rectal adenocarcinoma achieving near complete or complete response being managed by the Watch-and-Wait strategy. The primary end point being local regrowth and other survival and quality of life end points will be evaluated as well. A secure multinational database will be generated over 5 years with an estimated expected minimal sample size of 337 patients over 5 years across 7-10 Asian institutes to precisely evaluate the required endpoints. Ethical and legal requirements will be met at each participating institute.

1. INTRODUCTION AND RATIONALE

Neoadjuvant radiation and chemotherapy followed by total mesorectal excision (TME) remains a standard approach in most of the centres globally. Although the oncological outcomes have improved significantly with this multimodality approach over the last few decades, this approach adversely affects quality of life and functional outcomes especially for those needing permanent colostomy. More recently, patients achieving complete or near complete response are increasingly being managed by the 'Watch-and-Wait' approach where in, patients are followed using an intense follow up protocol after radiation and chemotherapy and avoid or delay surgery(1)(2)(3)(4)(5). However, this approach has not been widely adopted worldwide and there is limited data in the published medical literature. While the randomized trials in this setting does not appear to be feasible for obvious ethical reasons, robust data collected both retrospectively and prospectively can provide insights into this approach and help us refine the Watch-and-Wait approach in our routine clinics and in optimizing patient selection and surveillance strategies. Such an attempt was done by developing a multinational database from the Netherlands, Brazil, Portugal, and the UK(6). This data base consisted of more than a thousand patients and several important clinical questions were answered using this data(7)(8). However, this database largely consisted of patients treated using long course chemoradiation which was considered a standard treatment previously at that time. Moreover, there was no representation from Asian countries in this database. Currently, with the recent publications from the large, randomised trials like RAPIDO, UNICANCER PRODIGE 23, OPRA, more and more patients with locally advanced nonmetastatic rectal adenocarcinoma are managed with a total neoadjuvant therapy approach(9)(10)(11). Radiotherapy dose escalation using brachytherapy has also gained interest with recent publication of results from the OPERA trial(12). Hence, with these developments, management practice of locally advanced rectal adenocarcinomas has become heterogeneous across institutions globally. These patients are being treated with more aggressive neoadjuvant therapies including total neoadjuvant therapy (TNT) approach. Many of these regimens involve multiagent neoadjuvant chemotherapy in addition to chemoradiation or short course hypofractionated radiotherapy leading increased response rates. The knowledge about the risks and benefits of watch-and-wait strategy after newer neoadjuvant strategies is somewhat limited. It is not entirely known whether the watch-and-wait approach can be applied safely to these patients who achieve clinical complete response after more aggressive neoadjuvant therapy regimens. Also, the data on Asian patients managed with such a strategy is scarce in the literature. Not only the inherent biological and genetic factors associated with rectal adenocarcinoma in Asian patients may be different but also the compliance and feasibility of intense surveillance protocol can be challenging in some of the Asian countries. Considering all these, we intend to develop a comprehensive and secure database exclusively from Asian countries and to collect meaningful data systematically to answer important clinical questions on watch-and-wait strategy in Asian patients. This effort is likely to strengthen available evidence on this subject and generate evidence based on data exclusively from Asian patients. Collective efforts from participating nations can facilitate mutual learning and help in safe adoption of the watch-

and-wait strategy in a greater number of centres across Asia. This collaborative study among Asian countries may potentially pave the way for future studies of similar kind.

2. OBJECTIVES

Primary Objective

- To determine the local regrowth rates at 2 years in Asian patients managed with the watch-and-wait strategy after neoadjuvant therapy in rectal cancer.

Secondary Objectives

- To determine the rates of overall survival (OS) at 2 years and 5 years
- To determine disease free survival (DFS) at 2 years and 5 years
- To determine the rates of colostomy free survival at 2 years and 5 years
- To determine the clinical complete response rates (cCR) and regrowth rates with respect to various neoadjuvant treatment approaches
- To determine Quality of life (QOL) of patients managed with Watch-and-wait policy.
- To determine compliance of these patients to recommended surveillance protocol.

3. STUDY DESIGN

Prospective observational study

4. STUDY POPULATION

4.1 Population

4.2 Inclusion criteria

- Histologically confirmed diagnosis of adenocarcinoma of the rectum
- Age ≥18 years
- Clinical stage T1-T4, N0-N2, M0 at diagnosis
- ECOG Performance status 0-1
- Neoadjuvant treatment with either short course or long course radiation therapy and / or chemotherapy
- Complete or near complete clinical response after neoadjuvant therapy
- Patients willing to be on watch-and-wait strategy.
- The distance from anal verge of tumour up to 10 cm (Mid and low rectal tumours)

4.3 Exclusion criteria

- Recurrent rectal cancer
- Patients with any other concurrent medical or psychiatric condition or disease which would make them inappropriate candidates for entry into this study.
- Not willing to consent for the study or to follow up routinely

5. METHODS

5.1 Study objectives/endpoints

5.1.1 Main study objective/endpoint:

- To determine the local regrowth rates at 2 years in Asian patients managed with the watch-and-wait strategy after neoadjuvant therapy in rectal cancer.

5.1.2 Secondary objective/endpoints:

- To determine the rates of overall survival (OS) at 2 years and 5 years
- To determine disease free survival (DFS) at 2 years and 5 years
- To determine the rates of colostomy free survival at 2 years and 5 years
- To determine the clinical complete response rates (cCR) and regrowth rates with respect to various neoadjuvant treatment approaches
- To determine Quality of life (QOL) of patients managed with Watch-and-wait policy.
- To determine compliance of these patients to recommended surveillance protocol.

5.2 Study procedures

a. Participation of centres: Centres practicing watch-and-wait approach and willing to contribute to the database are invited to participate in this collaborative study. A central review committee will evaluate and approve the eligibility of the centre participating to ensure the quality of the data collected. Participating centres will be responsible for clearance and approval from local ethics boards and other regulatory bodies. A designated local Principal Investigator (PI) for individual site will be responsible for the regulatory formalities, participant accrual, data collection, storage and sharing of the data.

b. Participants satisfying eligibility criteria are invited to participate in this prospective observational study and will be included in the study after informed consenting process. Data will be collected prospectively by each participating centre and electronically uploaded on a secure database after pseudonymisation using REDCap software. A separate password protected datasheet for each institute will be maintained by respective local PI, however the Study Principal Investigator will be able to access the data.

c. Data variables to be collected include patient demographics, family history, personal history, symptomatology, clinical findings, stage and location of the tumour, histology, biomarkers, staging details, diagnostic imaging datasets (DICOM format), lab parameters, serial tumour marker levels, details of neoadjuvant radiation and chemotherapy, response assessment findings, surveillance imaging and endoscopic images, treatment details for regrowth or

relapse, need for colostomy etc. The data is collected up to 5 years after enrolment.

d. No investigations or therapeutic interventions will be done as a part of this study and the nature of the study remains observational only.

5.3 Withdrawal of individual subjects

Participants have the right to withdraw any time after consenting and the data will not be collected any further after withdrawal. However, the data collected up till the withdrawal can be used for analysis.

5.4 Follow-up of subjects withdrawn from treatment

The follow up of the patients after withdrawal will continue as per standard of care as this is an observational study.

6. SAFETY REPORTING

6.1 AEs, SAEs and SUSARs: Not applicable as this is an observational study.

6.2 Data Safety Monitoring Board (DSMB) / Safety Committee

The study will be monitored by an independent data safety monitoring committee from the respective institute as per guidance of the institutional review board.

7. STATISTICAL ANALYSIS

Sample Size justification: The primary objective of the study is to evaluate the local regrowth at 2 years reduces in watch-and-wait patients as compared to surgery patients. Considering a local regrowth rate of 25% it is estimated that approximately 306 patients are required to be included in the study to achieve a precision of 10% at 5% level of significance and 80% power without attrition. Assuming 10% attrition rate a total of 337 patients will be required for the study. This appears feasible expecting a contribution of 35-70 patients each over 3 years from about 7-10 centres across Asia.

7.1 Primary study parameter (Definitions)

- Local regrowth rate: Rate of local regrowth at 2 years from the date of diagnosis to date of regrowth

7.2 Secondary study parameters (Definitions)

- Rates of overall survival at 2 years and 5 years is measured as a time to event end point from the date of diagnosis to date of death from any cause
- Disease free survival at 2 years and 5 years measured as a time to event end point from the date of diagnosis to date of relapse or death from any cause
- Colostomy free survival at 2 years and 5 years is measured as a time to event end point from the date of diagnosis to date of colostomy or date of death from any cause
- Clinical complete response rates and regrowth rates with respect to various neoadjuvant treatment approaches
- Quality of life using EORTC QLQC30 and QLQCR29 questionnaire at baseline, 3 months, 6months then 6 monthly for 2 years.
- Compliance of these patients to recommended surveillance protocol

7.3 Statistical Analysis Plan:

Continuous variables will be summarized with descriptive statistics Mean (SD) or Median (IQR). Categorical variables will summarize with frequency and percentage.

The local regrowth rate at 2yrs will be obtained using Kaplan Meier Estimator and the local regrowth will be compared in two arms using log rank test.

Survival endpoints like OS and DFS rates at 2years will be estimated using Kaplan Meier Method and comparison for factors will be done using log rank Test. Multivariate analysis will be carried out using cox regression based on the factors identified in the univariate analysis by maintaining the variable to event ratio. The Clinical Complete Response will be reported using proportions and will be compared between two arms using Chi Square test. P value of less than 0.05 will be considered significant. All statistical analysis will be conducted using SPSS ver.25.

8. ETHICAL CONSIDERATIONS

8.1 Recruitment and consent

Before commencing the study, the protocol is subjected to review and approval by the local Research Ethics Committee in accordance with national guidelines and legislation. Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West, and Edinburgh amendments) or the laws and regulations of the country, whichever provides the greatest protection to the patient will be followed. Patient information sheets will be produced in all the relevant languages to eligible participants after screening in routine clinics. All patients will be informed of the aims of the study, the possible adverse events, the procedures, and possible hazards to which he/she will be exposed. It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care.

8.2 Considerations for incapacitated subjects or vulnerable population (if applicable)

Not applicable

8.3 Benefits and risks assessment.

This is an observational study with no interventions done as a part of study. There are no direct benefits and risks to the participant. However, the data could add to the current knowledge about outcome of patients in such clinical settings and further help in optimizing the management of these patients in future based on the results of the study.

8.4 Compensation for injury

As this is an observational study, there is no compensation applicable.

8.5 Incentives (if applicable)

No incentive will be provided to participants.

9. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

9.1 Handling and storage of data and documents

Subject identification: The name of the patient will not be asked for nor recorded at the Study Office. A sequential identification number will be automatically attributed to each patient registered in the trial. There will be an additional identifier denoting the institute. This number will identify the patient and must be included on all case record forms.

They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for study purposes by authorized individuals other than their treating physician. Documented informed consent must be obtained for all patients included in the study before they are registered at the Study Office. This must be done in accordance with the national and local regulatory requirements.

9.2 Monitoring and Quality Assurance

The study will be monitored by an independent data and safety monitoring committee.

9.3 Publication policy

Investigator from the Institution contributing data for >10 patients will be considered for the authorship provided the investigator is willing to review and approve the final manuscript and satisfy authorship criteria and per journal requirements.

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