**CLINICAL STUDY PROTCOL**

**Title: Improved survival after multidisciplinary team** **decision-making for patients with advanced gastrointestinal cancer: A multicenter, prospective, noninterventional, controlled study**

**Principle Investigator：**Jian Li

Department of GI Oncology,

Laboratory of Carcinogenesis and Translational Research of the Ministry of Education,

Peking University School of Oncology,

Beijing Cancer Hospital & Institute,

Beijing, China

E-mail：oncogene@163.com

Tel: +86-10-88196561

Fax: +86-10-88196561

Table of Conetent

[1. Background 4](#_Toc57016484)

[1.1 Multidisciplinary team 4](#_Toc57016485)

[1.2 The research status of MDT in the world 4](#_Toc57016486)

[1.3 The research status of MDT in China 5](#_Toc57016487)

[2. Objectives of the study 7](#_Toc57016488)

[2.1 Primary objective 7](#_Toc57016489)

[2.2 Secondary objectives 7](#_Toc57016490)

[2.3 Exploratory Objectives 7](#_Toc57016491)

[3. Subjects 7](#_Toc57016492)

[3.1 Inclusion criteria 7](#_Toc57016493)

[3.2 Exclusion Criteria 8](#_Toc57016494)

[4. Participation medical centers 9](#_Toc57016495)

[5. Study Methods 10](#_Toc57016496)

[5.1 Study Design 10](#_Toc57016497)

[5.2 Planned length of study 10](#_Toc57016498)

[5.3 Planned Sample Size 10](#_Toc57016499)

[5.4 Statistical analysis 11](#_Toc57016500)

[5.5 Endpoint 11](#_Toc57016501)

[5.5.1 Primary Endpoint 11](#_Toc57016502)

[5.5.2 Secondary Endpoints 12](#_Toc57016503)

[6. Data collection 12](#_Toc57016504)

[6.1 Participation Medical Centers’ information 12](#_Toc57016505)

[6.2 Enrolment Patients’ information 12](#_Toc57016506)

[6.3 Disease information 13](#_Toc57016507)

[6.4 MDT discussion information 13](#_Toc57016508)

[6.5 Interview information 13](#_Toc57016509)

[7. Study procedure 13](#_Toc57016510)

[7.1 Subjects Screening 14](#_Toc57016511)

[7.2 MDT discussion 14](#_Toc57016512)

[7.3 Visiting during the study 14](#_Toc57016513)

[8. Data Administration 15](#_Toc57016514)

[8.1 Database 15](#_Toc57016515)

[8.2 Data entry 15](#_Toc57016516)

[References: 16](#_Toc57016517)

# 1. Background

## 1.1 Multidisciplinary team

Multidisciplinary team (MDT) meeting, also known as tumour board, is composed of specialists from two or more related disciplines, which discuss and formulate patient-specific treatment recommendations[1, 2]. Tumor board were initially created in the USA in the 1970, with the primary goal of educational rather than aiming to improve patient care[2]. And MDT concept was popularized and shifted in focus towards delivery of care, after the Calman-Hine report in the UK, which recommended the coordination within MDT regarding the treatment of colorectal cancer (CRC) in 1995[3]. After decades of development, several countries have formed a relatively perfect MDT mode, which has been the one of basic principles of cancer treatment.

## 1.2 The research status of MDT in the world

Although the MDT mode is recommended for the diagnosis and treatment of a variety of solid tumours, the studies to investigate the most appropriate mode for cancer patients, especially the effective implementation rate of the MDT decisions and whether it can bring benefits to cancer patients, are very limited, and results mainly came from retrospective studies with small sample sizes.

A study of breast cancer showed that 6.9% of MDT decisions (n=289) was not implemented, and the frequent reasons for nonimplementation were because of patient preferences (65%, n=13) and individual doctor’s view (20%, n=4). Besides, the proportion of elderly patients refusing MDT decisions was significantly increased[4]. Another MDT study of CRC showed that 10% of decisions were not implemented, with 40 % of reasons for nonimplementation relating to co-morbidity and 35% to patient choice[5].

And one of the few studies aiming to explore survival benefits of MDT in CRC patients with radical surgery was form the UK, and showed that a significantly great number of patients was prescribed adjuvant chemotherapy in MDT group than that in not-MDT group. Furthermore, three-year survival for Duck C patients was increased significant in MDT group than those in not-MDT group[6].

## 1.3 The research status of MDT in China

After the concept of MDT had been introduced firstly in China in 2005, it has gradually got the attention of the government, academic groups, doctors and patients until recent years, and six medical centers were selected as colorectal cancer MDT demonstration bases to promote the MDT mode to the whole country. And several cancer treatment consensuses began to make suggestions of diagnosis and treatment by MDT, mainly involved gastrointestinal cancers in China[7, 8]. As one of the first hospitals to organize the MDT discussion in China, we have reported that MDT discussion can significantly improve the outcomes of patients with early and locally advanced gastric and colorectal cancer[9].

However, with uneven level of medical centers and the large disparity of patients to pay for medical expenses, it is more difficult to implement MDT discussion in China than in western countries. Besides, is the current MDT mode really suitable for cancer patients? How is the acceptability and what is implementation rate? The reason for failure to implement MDT decisions is because the medical technology, or insufficient recognition of doctors and patients to the MDT mode? More importantly, does this mode really provide the survival benefit for patients? These critical questions related to the quality of the MDT mode have not yet been explored, and hard to answer. Therefore, the study of MDT mode under the real medical practice has important significance for improving the current MDT mode and further improving the survival of cancer patients.

Here, we carry out a prospective MDT study to evaluate the impact of MDT decision-making on the survival of patients with advanced gastrointestinal cancer by grouping them according to their implementation of MDT decisions.

# 2. Objectives of the study

## 2.1 Primary objective

To evaluate the impact of implementation MDT decisions on the overall survival of patients with advanced gastrointestinal cancer

## 2.2 Secondary objectives

1) To evaluate the implementation rate of MDT decisions;

2) To evaluate the reasons for not implementing MDT decisions;

3) To evaluate the MDT of patients with different tumor type;

## 2.3 Exploratory Objectives

To provide a general overview of the MDT in China and optimize the current MDT mode;

# 3. Subjects

## 3.1 Inclusion criteria

1. Be willing and able to provide written informed consent for the trial;
2. Adult age of 18 years and older；
3. Sex：Male or female;
4. Histologically or cytologically confirm advanced gastrointestinal malignancies；
5. Estimated life expectancy 12 weeks；
6. A baseline Eastern Cooperative Oncology Group performance status of 0-2；
7. Adequate hematopoietic function of bone marrow (within 7 days prior to MDT): hemoglobin 9g/dL, white blood cells ≥ 3.0 × 109 / L, neutrophils ≥ 1.5 × 109 / L, platelets ≥ 100 × 109 / L; normal liver and kidney function (within 14 days prior to MDT): TBIL ≤ 1.5 upper limit of normal (ULN); ALT and AST ≤ 2.5 ULN; for patients with liver metastases, ALT and AST ≤ 5 ULN; creatinine ≤ 1.5 ULN;
8. Normal cardiopulmonary function;
9. More than two disciplines participation the MDT discussions；

## 3.2 Exclusion Criteria

1. Early or locally advanced tumour;
2. Primary malignant tumour other than gastrointestinal cancer;
3. Active severe infection, including active tuberculosis, within 14 days before enrolment;
4. Clinically significant cardiovascular diseases that, in the opinion of investigator, made patients not appreciated for any anti-tumor treatment, such as heart failure (NYHA III-IV), uncontrolled coronary heart disease, cardiomyopathy, uncontrolled arrhythmia, uncontrolled hypertension or a history of myocardial infarction;
5. Neurological or psychiatric disorders affecting cognitive function, including central nervous system metastases;
6. Uncontrolled systemic diseases, such as poorly controlled diabetes mellitus;
7. Pregnancy (determined by serum beta-chorionic gonadotropin test) or breastfeeding.;

# 4. Participation medical centers

1. Beijing Cancer Hospital
2. Fudan University Shanghai Cancer Center
3. The First Affiliated Hospital of Zhengzhou University
4. The First Affiliated Hospital of Zhejiang University
5. The First Affiliated Hospital of Nanjing Medical University
6. Affiliated Drum Tower Hospital of Nanjing University
7. Liaoning Cancer Hospital
8. The First Hospital of China Medical University
9. Second Affiliated Hospital of Zhengzhou University
10. The Third People’s hospital of Zhengzhou
11. West China Hospital of Sichuan University
12. Peking University People's Hospital
13. Port Hospital of Hebei Port Group Co.Ltd.

# 5. Study Methods

## 5.1 Study Design

This is a prospective, multicenter, noninterventional, controlled study to evaluate the survival benefit and implementation of MDT in patients with metastatic gastrointestinal cancer.

## 5.2 Planned length of study

1) Length of recruitment: 12 months

2) Total study length: 24 months

## 5.3 Planned Sample Size

Taking into consideration the current medical situation in China, it was estimated that the proportion of patients who implemented MDT decisions was about 70%. Assuming the hazard ratio (HR) of 0.70 for the MDT decision implementation over nonimplementation group, it would be necessary to include approximately 421 patients (implementation group: 295 patients; nonimplementation group:126 patients) to provide an 80% statistical power with a two-sided *P* value of 0.05 indicating statistical significance, considering about 15% loss to follow-up.

## 5.4 Statistical analysis

Statistical analyses were carried out using SPSS version 26.0 (SPSS Inc., IL, USA). All characteristics will be described by the frequency for categorical variables, by the mean and standard deviation for normally distributed continuous data, and by the median for non-normally distributed continuous data. Survival data was estimated using the Kaplan–Meier method and compared with the log-rank test. Cox proportional hazards regression models were used to estimate HR and 95% CI for variables associated with survival data. P values of less than 0.05 will be taken to indicate statistically significant differences.

## 5.5 Endpoint

### 5.5.1 Primary Endpoint

Overall survival

### 5.5.2 Secondary Endpoints

1) The implementation rate of MDT decisions

2) subgroup analysis of different tumor types

# 6. Data collection

## 6.1 Participation Medical Centers’ information

Information about the involved medical centers, length of time of MDT conducted, number of annual MDT discussion, proportion of associated chief physician or above involved, the fee of MDT discussion will be collected before the MDT discussion.

## 6.2 Enrolment Patients’ information

Information about the sex, age, occupation, marital status, religious belief, medical treatment location (local/non-local), education level, way to pay medical care (medical insurance and self-payment), number of visits before MDT, MDT applicant disciplines, and patient's knowledge of the MDT mode will be collected before MDT discussion.

## 6.3 Disease information

Information about the primary tumor location, staging, diagnosis time, timing of MDT (first-time consultation or further consultation before submitted to MDT), number of prior chemotherapy lines, and aim of MDT discussion will be collected before MDT discussion.

## 6.4 MDT discussion information

Information about the date of MDT discussion, duration of MDT discussion, number of involved disciplines, and final MDT decision, and final decision discipline, will be collected during MDT discussion.

## 6.5 Interview information

Information about the medical center of implementing the MDT decision, the patient's recognition of MDT decision, the implementation status of MDT decision, and the reasons for not implementing MDT, and survival status will be collected after MDT discussion.

# 7. Study procedure

Prior to the initiation ant screening or study-specifical procedures, patients have to read and voluntarily sign the informed consent, approved by the Independent Ethics Committee, and should be willing and able to comply with parameters as outlined in the protocol.

## 7.1 Subjects Screening

Screening procedure should be completed within three day before MDT discussions (including the day of MDT)

1. Patients sign the informed consent;
2. Collection the demographic characteristics and previous process of diagnose and treatment for patients

## 7.2 MDT discussion

Collecting the information of MDT discussion

## 7.3 Visiting during the study

1. Patient's recognition of MDT decision and the willingness to implement decision was collected with one week after MDT;
2. The preliminary implementation status of MDT decisions and the reasons for not implementation will be collected within one month after the MDT discussion.
3. For patients who are willing to implement MDT decisions, the specific treatment process that patients received will be collected every month.
4. After patients finishing implementing the MDT decisions or clearly refusing to implement the decisions, survival status will be visited every three months.

# 8. Data Administration

## 8.1 Database

All data of each patient should be completely entered into the database, and the data will be shared by investigators of all participating centers.

## 8.2 Data entry

1. The principal investigators of the involved medical centers should be responsible for the data entry and administration.
2. All the data of patients will be entry carefully and in detail.
3. The data will be regarded as the original data and should not be changed at will;

# References:

[1] Øvretveit, John, Five ways to describe a multidisciplinary team, Hol Medicine, 10 (1996) 163-171.

[2] H.L. Berman, The tumor board: is it worth saving?, Mil Med, 140 (1975) 529-531.

[3] Dec, A Policy Framework for Commissioning Cancer Services : A Report by the Expert Advisory Group on Cancer to the Chief Medical Officers of England and Wales.

[4] R. English, C. Metcalfe, J. Day, Z. Rayter, J.M. Blazeby, A prospective analysis of implementation of multi-disciplinary team decisions in breast cancer, The breast journal, 18 (2012) 459-463.

[5] J.J. Wood, C. Metcalfe, A. Paes, P. Sylvester, P. Durdey, M.G. Thomas, J.M. Blazeby, An evaluation of treatment decisions at a colorectal cancer multi-disciplinary team, Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland, 10 (2008) 769-772.

[6] E. MacDermid, G. Hooton, M. MacDonald, G. McKay, D. Grose, N. Mohammed, C. Porteous, Improving patient survival with the colorectal cancer multi-disciplinary team, Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland, 11 (2009) 291-295.

[7] P. Song, Q. Wu, Y. Huang, Multidisciplinary team and team oncology medicine research and development in China, Bioscience trends, 4 (2010) 151-160.

[8] J. Lu, Y. Jiang, M. Qian, L. Lv, X. Ying, The Improved Effects of a Multidisciplinary Team on the Survival of Breast Cancer Patients: Experiences from China, Int J Environ Res Public Health, 17 (2019).

[9] C.-Z. Du, J. Li, Y. Cai, Y.-S. Sun, W.-C. Xue, J. Gu, Effect of multidisciplinary team treatment on outcomes of patients with gastrointestinal malignancy, World journal of gastroenterology, 17 (2011) 2013-2018.