



UMEÅ UNIVERSITET

Umeå University Medical Dissertations, New Series No 2124

Mismatch Repair Deficiency in Colorectal Cancer

Prognosis and prediction for basic treatment strategies

Ioannis Gkekas

Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för
avläggande av filosofie/medicine doktorsexamen framläggs till
offentligt försvar i Betula, Byggnad 6 M plan 0, Norrlands
Universitetssjukhus.

Fredagen den 11:e Juni, kl. 13:00.

Avhandlingen kommer att försvaras på svenska.

Fakultetsopponent: Docent, Christian Sturesson,
Department of Clinical Science, Intervention and Technology,
Stockholm, Karolinska institute, Sverige.

Department of Surgery and Perioperative Sciences
Department of Medical Biosciences

Organization

Umeå University
Department of Surgery
And Perioperative Sciences
Department of Medical Biosciences

Document type

Doctoral thesis

Date of publication

21 May 2021

Author

Ioannis Gkekas

Title

Mismatch Repair Deficiency in Colorectal Cancer
Prognosis and prediction for basic treatment strategies

Abstract

Colorectal cancer (CRC) remains a significant healthcare problem world-wide, being the third most common cancer and the fourth most frequent cause of cancer death. Among genetic aberrations involved in CRC carcinogenesis, defective mismatch repair (dMMR) is one of the major pathways. Mismatch repair (MMR) plays a critical role in the repair of errors that occur spontaneously during DNA replication, such as single base mismatches, short insertions or deletions. dMMR increases mutation frequency in an affected cell approximately 1000 times, leading to microsatellite instability (MSI) through the accumulation of short repetitive DNA sequences called microsatellites. Carcinogenesis in dMMR cases can present as hereditary cases (Lynch syndrome) due to germline mutation in one of the main MMR genes – *MLH1*, *MSH2*, *MSH6*, and *PMS2* or somatic/sporadic cases (epigenetic silencing or somatic inactivation of *MLH1* promoter).

The aim of this thesis is to assess the latest publications about the role of MSI status as prognostic factor in stage II colon cancer patients (study I), to validate the application of the MMR status as a prognostic factor in patients with colon cancer stage II (study II), as a predictive factor in relation to the administration of adjuvant chemotherapy in patients with stage II colon cancer (study III), to investigate the potential role of MMR status as a risk factor for emergency colorectal surgery (study IV), and finally to investigate the association between CRC with sporadic dMMR and non-colorectal malignancies (study V).

Study I revealed that MSI in stage II colon cancer patients don't correlate with significantly better overall survival (OS), neither disease free survival (DFS) in the last published studies.

Study II verify the prognostic role of MMR status in stage II patients with colon cancer. Patients with dMMR tumors have a significantly lower risk for tumor recurrence. This relationship doesn't correlate to better OS as these patients are older and suffer other causes of death than cancer related.

Study III showed the predictive role of MMR status in stage II patients with colon cancer. Patients with proficient MMR (pMMR) status receiving adjuvant chemotherapy have a significantly better OS than those given no treatment. This relationship was not detected in patients with dMMR tumors. Especially patients with pMMR tumors that received adjuvant treatment have a significantly longer survival time after the first relapse compared with those not receiving treatment.

Study IV revealed a higher risk of colon cancers with dMMR status to undergo acute surgery. Other variables that revealed same relationship were tumors Stage III and IV.

Study V showed that CRC patients with sporadic dMMR tumors present a higher incidence to the occurrence of a second non-colorectal cancer prior to or after the presentation of the CRC tumor. It might be advantageous to screen patients with dMMR tumors for other cancers in another setting than that used for the general population.

Keywords

Colorectal cancer, Mismatch Repair, prognosis, prediction, acute surgery, sporadic cancer

Language

English

ISBN

978-91-7855-498-0 (tryck)

978-91-7855-499-7 (PDF)

ISSN

0346-6612

Number of pages

62 + 5 papers