

Macrophages in colorectal cancer: proof of principle for diagnostic application

Citation for published version (APA):

Japink, D. (2015). *Macrophages in colorectal cancer: proof of principle for diagnostic application*. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20150424dj>

Document status and date:

Published: 01/01/2015

DOI:

[10.26481/dis.20150424dj](https://doi.org/10.26481/dis.20150424dj)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

1.3 Monitoring relevance

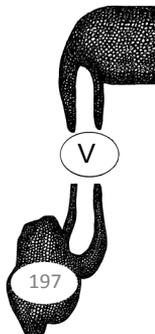
Monitoring response to neoadjuvant treatment in rectal cancer patients could enable identification of responders and non-responders before or early during neoadjuvant therapy⁷. In combination with blood biomarkers this additional value was reported in a prediction model utilised before neoadjuvant treatment⁸. In our studies it was shown that the added value could be increased even further (AUC 0.94), by adding monocyte and macrophage analyses in combination with other serum markers and PET-CT values to a prediction model during the first two weeks of neoadjuvant treatment. When evaluating these outcomes upfront in all rectal cancer patients, the patients benefitting from neoadjuvant treatment could be identified. The patients who would not benefit could be treated according to other protocols or specific patients could refrain from therapy at all. These emerging options would lead to personalised medicine, that could lead to better quality of life for rectal cancer patients, and more appropriate spending of resources.

2. Target groups, activities and products

The medical specialities who could utilise the outcomes of this thesis are the gastroenterologists and surgeons treating CRC patients. Immunologists could utilise the outcomes to further investigate the role of macrophages and monocytes in immunocompetence in cancer in general and specifically in CRC. When proven useful, development of an immuno-competence assay for cancer patients could be the next step. Oncologists could incorporate immunological assays (such as the EDIM-assay) in cancer follow-up settings for disease monitoring purposes. Finally, Radiotherapists could first investigate and at a later time point include monocyte and macrophage measurements, utilising the EDIM method, in treatment monitoring settings. National and global funding organisations should recognise the potential of immunological cancer research and expand their funding capacity towards this part of medical research. Participation of other (UM-) parties in further development of this assay could accelerate the development and broaden the applicability in medicine.

3. Innovation

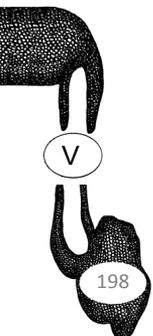
The EDIM-method is a completely new way of utilising cells of the immune system, such as monocytes and macrophages, for diagnostic, follow-up and



monitoring purposes. In prostate cancer this method was first described for diagnostic purposes by Herwig et al.⁹⁻¹² and confirmed by Leers et al. in 2008¹³. The basic question of the actual localisation of tumour markers in macrophages was investigated by our group using the colorectal cancer model. Utilising light and electron microscopy the localisation of the antibody against CEA inside the monocytes and macrophages was visualised and confirmed^{14,15}. In a pilot setting this innovative method was applied in a CRC diagnostic setting showing distinguishing capabilities between healthy and CRC patients. Addition of CRP allowed distinguishing CRC patients from benign inflammatory diseases of the colon¹⁶. Validation of such an assay is innovative. All parts of the validation process must be conceived, tested and applied. This process has been performed and reported by our group¹⁷. The potential of applying the assay in CRC follow-up (research in progress) and in monitoring rectal cancer (paper submitted) has been and is currently being explored by our research group. The value of the EDIM-method in comparison to established diagnostic tools and other experimental methods in cancer diagnostics needs further evaluation.

4. Planning and realisation

Studies as described above are currently performed or have been performed with the results being published soon.



5. References

1. American Cancer Society. The global economic cost of cancer. *acspsc-026203.pdf*. 2010;.
2. Society AC. Cancer Facts & Figures 2014. American Cancer Society Atlanta; 2014;.
3. Hoeveel zorg gebruiken mensen met kanker en wat zijn de kosten? [[Internet]]. Nationaal Kompas Volksgezondheid. [cited 2014]. Retrieved from: <http://www.nationaalkompas.nl/gezondheid-en-ziekte/ziekten-en-aandoeningen/kanker/hoeveel-zorg-gebruiken-mensen-met-kanker-en-kosten/>
4. Penning C. Landelijke monitoring van het bevolkingsonderzoek darmkanker: resultaten eerste halfjaar 2014. 2014;.
5. Duffy MJ, Lamerz R, Haglund C, Nicolini A, Kalousová M, Holubec L, and Sturgeon C. Tumor markers in colorectal cancer, gastric cancer and gastrointestinal stromal cancers: European group on tumor markers 2014 guidelines update. *Int J Cancer*. 2013;.
6. Kievit J. Follow-up of patients with colorectal cancer: numbers needed to test and treat. *Eur J Cancer*. England; 2002;38(7):986-99.
7. van Stiphout RG, Lammering G, Buijsen J, Janssen MH, Gambacorta MA, Slagmolen P, Lambrecht M, Rubello D, Gava M, Giordano A, Postma EO, Haustermans K, Capirci C, Valentini V, and Lambin P. Development and external validation of a predictive model for pathological complete response of rectal cancer patients including sequential PET-CT imaging. *Radiother Oncol*. Ireland; 2011;98(1):126-33.
8. Buijsen J, van Stiphout RG, Menheere PP, Lammering G, and Lambin P. Blood biomarkers are helpful in the prediction of response to chemoradiation in rectal cancer: A prospective, hypothesis driven study on patients with locally advanced rectal cancer. *Radiother Oncol*. 2014;.
9. Herwig R, Djavan B, Kramer G, El-Taieb MA, Kuhhas F, Leers M, and Marberger M. [Prostate cancer screening with a new marker based on circulating blood macrophages?]. *Urologe A*. 2007;46(9):1066-70.
10. Herwig R. Measurement of intracellular versus extracellular prostate-specific antigen levels in peripheral macrophages: a new approach to noninvasive diagnosis of prostate cancer. *Clin Prostate Cancer*. 2004;Dec;3(3):184-8.
11. Herwig R, Mitteregger D, Djavan B, Kramer G, Margreiter M, Leers MP, Glodny B, Haider DG, Hörl WH, and Marberger M. Detecting prostate cancer by intracellular macrophage prostate-specific antigen (PSA): a more specific and sensitive marker than conventional serum total PSA. *European journal of clinical investigation*. Wiley Online Library; 2008;38(6):430-437.
12. Herwig R, Horninger W, Rehder P, Klocker H, Ramoner R, Thurnher M, Pinggera GM, Gozzi C, Konwalinka G, and Bartsch G. Ability of PSA-positive circulating macrophages to detect prostate cancer. *The Prostate*. Wiley Online Library; 2005;62(3):290-298.
13. Leers MPG, Nap M, Herwig R, Delaere K, and Nauwelaers F. Circulating PSA-Containing Macrophages as a Possible Target for the Detection of Prostate Cancer. *American journal of clinical pathology*. American Society for Clinical Pathology; 2008;129(4):649.
14. Japink D, von Meyenfeldt MF, Nap M, Sosef MN, Verheyen F, Beets GL, and Leers MPG. Visualizing CEA in activated macrophages using electron microscopy. (submitted). 2014;.
15. Faber TJ, Japink D, Leers MP, Sosef MN, von Meyenfeldt MF, and Nap M. Activated macrophages containing tumor marker in colon carcinoma: immunohistochemical proof of a concept. *Tumour Biol*. Netherlands; 2011;33(2):435-41.
16. Japink D, Leers MPG, Sosef MN, and Nap M. CEA in activated macrophages. New diagnostic possibilities for tumor markers in early colorectal cancer. *Anticancer research*. International Institute of Anticancer Research; 2009;29(8):3245.
17. Japink D, Nap M, Sosef MN, Nelemans PJ, Coy JF, Beets G, von Meyenfeldt MF, and Leers MP. Reproducibility studies for experimental epitope detection in macrophages (EDIM). *J Immunol Methods*. Netherlands; 2014;407:40-7.

