Rectal cancer: steps towards tailored treatment

Chapter 11

Valorization

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Cancer is the leading cause of death in the Netherlands and its incidence is expected to increase substantially in the coming years. This expected rise in cancer incidence is even more pronounced due to the increasing proportion of elderly in the population and the increased life expectancy. Colorectal cancer is the second most occurring cancer type in men and the third in women. This makes rectal cancer an important health care problem.

Although the results of rectal cancer treatment have been improved substantially in the last decades, there is certainly room for improvement. Traditionally, cancer treatment has been based on clinical staging, which is a rather rough classification and results in an important percentage of under- and overtreatment. Rectal cancer treatment has been characterized by a tendency to overtreatment in the Netherlands in the last years, resulting in an increased risk of long-term sequelae and higher costs. Furthermore, it is expected that the distribution of clinical stages at the time of diagnosis will shift to earlier stages in the coming years, due to the recent introduction of a national screening program for bowel cancer. The most important themes in Dutch healthcare at this moment are control of costs, improvement of quality and shared decision-making. These considerations all ask for soundly based individualization of treatment.

The main theme of this thesis is the development of more tailored treatment of rectal cancer. This tailoring of treatment can consist of an intensification of treatment for patients who will benefit from it and a de-escalation of pre-operative treatment in patients who have very sensitive tumors or who do not need neo-adjuvant treatment at all. To make it even more complex, treatment intensification can have two different aims: a better chance of locoregional control or a higher chance of complete response, opening the way to organ preservation. Although more information is needed about long-term outcome of oncological outcome of organ-preserving treatment, it has important advantages: post-operative complications are avoided, possible toxicity caused by the surgical intervention (fecal urge and incontinence, urinary incontinence,

sexual dysfunction) does not occur and a colostomy can be avoided. This is expected to lead to less healthcare costs and a better quality of life. Therefore, if oncological safety of the watch-and-wait approach in clinical complete responders can be confirmed, it may become the ultimate goal of (chemo)radiotherapy in rectal cancer treatment.

Relevance of the scientific results of this thesis

The results presented in the first part of this thesis can be seen as a step in the development of boost techniques for radiotherapy in rectal cancer. Dose escalation is one possibility to increase the chance of a complete response in radiotherapy. The studies presented in this thesis have proven that PET-CT is a reliable and reproducible method for adequate delineation of the primary tumor, a prerequisite for tumor boosting.

The second part of this thesis presents the first steps in the development of predictive models for rectal cancer treatment. PET-scan has been proven to be a strong instrument in response prediction in rectal cancer treatment. The work presented here was a first indication that PET-information has predictive value. The nomogram has been made available online (www.predictcancer.org). Based on these results, we developed a program aimed at the optimal use of PET-scan in predictive models for rectal cancer. In the meantime, our group has published more articles about the use of PET for early response evaluation and we have found that PET-scan after 2 weeks of treatment is able to separate good responders from bad responders. This concept has been validated in a prospective multicenter trial.

The studies discussed in the third and last part were aimed at treatment intensification. Both studies are examples of early translation of laboratory findings into clinical practice. The second particularity of these 2 studies is the use of drugs that were registered already for other indications. The advantage of this approach is not only that the side effects of these drugs are well known, but also that the costs are substantially lower than the costs of recently developed and patented drugs. Unfortunately the combination of nelfinavir and

chemoradiation turned out to have an unfavorable toxicity profile and the distribution of nelfinavir was stopped in the Netherlands, which made us decide not to go on to phase II. The combination of rapamycin and radiotherapy was well tolerated if surgery was delayed, but our hypothesis could not be confirmed. Although rapamycin had a clear biological activity in rectal cancer, as reflected by the SUV-changes on PET-scan, this did not translate into a substantial increase in response. Therefore, the scheme as tested in this phase I/II trial is not promising enough to continue to a phase III trial.

Innovation and future

The principle of response prediction has been shown to be feasible in clinical practice. We therefore want to further explore the possibilities in clinical practice by adapting treatment based on early response prediction to increase the response rates. The use of prediction models allows us to intensify treatment only in patients who have a high chance to benefit from it, which is a new approach as compared to the “one-size-fits-all” recommendations in guidelines. Another important goal for future projects is to incorporate patient preferences into treatment decisions. This process will also be supported by reliable response prediction.