Imaging and biomarkers to aid in treatment decisions in melanoma and rectal cancer

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General introduction and outline of the thesis

General introduction

Melanoma

Melanoma is the most aggressive form of skin cancer. It has strong tendency to metastasize. The incidence of melanoma has increased rapidly over the past decades and is still rising. It is currently the fifth most common cancer in men and women in western countries.[1] Sun and ultraviolet exposure are major risk factors and the continuous rise in incidence can, in part, be explained by the change in sun-bathing behavior, the increasing use of tanning beds and the aging of the population.[2, 3] Despite the increase in incidence, the number of melanoma-related deaths has not increased proportionally. This can largely be explained by improvements in early detection and excision of primary tumors and by increased awareness among primary care providers and the general population. The availability of newer forms of systemic treatment for advanced melanoma in the past decade have further lowered the mortality of this disease.

For decades, chemotherapy was the only systemic treatment option for metastatic melanoma. The prospects for patients with metastatic disease were poor, with a median survival of only 6-9 months and a 5-year survival rate of approximately 6%.[4] In the past decade, treatment of metastatic melanoma was revolutionized by the introduction of two new classes of systemic treatment: BRAF-targeted therapy and immunotherapy. B-Raf is a protein kinase that acts as a signaling protein in the MAPK pathway. It is mutated in forty-five percent of the patients with cutaneous melanoma.[5] BRAF mutations in the V600 region results in a hyperactive state of the protein that drives oncogenesis. Vemurafenib, dabrafenib and encorafenib are specific BRAF-V600 inhibitors that directly inhibit tumor growth and produce rapid responses in nearly 50% of BRAF-mutated melanoma patients.[6, 7] An overall survival benefit was shown compared to dacarbazine chemotherapy resulting in regulatory approval. Despite the impressive responses to BRAF inhibitors, acquired resistance to treatment by reactivation of the MAPK pathway develops in almost all patients.[8] To delay treatment resistance, the effect of blocking two signaling proteins in the MAPK pathway was explored. The combination of BRAF and MEK inhibitors demonstrated higher response rates and improved survival compared to BRAF inhibitor monotherapy and became the standard for targeted therapy of BRAF-mutated melanoma.[9, 10]

The development that dramatically changed the treatment of metastatic melanoma was the introduction of immune checkpoint inhibitors. The importance of immune responses in melanoma has long been recognized. Immune stimulatory treatment with high-dose IL2 showed durable responses in a small subset of patients but because its use was limited by high toxicity it never became standard treatment.[11] The recognition of the importance of immune checkpoints, costimulatory and –inhibitory receptors on T cells and antigen-

presenting cells in cancer immune surveillance led to the development of immune checkpoint inhibitors. Ipilimumab, a CTLA-4 blocking monoclonal antibody, was the first immune checkpoint inhibitor that improved overall survival and because of a survival benefit over treatment with dacarbazine it gained regulatory approval for treatment of advanced melanoma.[12] Although objective responses to ipilimumab were limited to 11% of the patients, the responses were often durable and these long-lasting responses possibly represent 'cure' of melanoma.[13] After ipilimumab, the PD1-blocking monoclonal antibodies nivolumab and pembrolizumab were approved based on phase 3 trials that showed better overall survival compared to both chemotherapy and ipilimumab.[14-16] The combination of the immune checkpoint inhibitors ipilimumab and nivolumab, improved survival even further compared to single-agent treatment.[17] 5-year overall survival rate in patients with metastatic melanoma treated with this treatment combination is around 50% and responses appear to be very durable.[18] Recently, immunotherapy with nivolumab or pembrolizumab and, in case of a BRAF-mutated melanoma, the combination of dabrafenib and trametinib have been approved in Europe in the adjuvant setting after surgical resection of stage III melanoma.[19-21]

Although the survival of patients with advanced melanoma has dramatically improved with the aforementioned systemic treatments, there are unanswered questions about how they should be applied and sequenced with local therapy in clinical practice. Melanoma metastases in brain and intestine are frequently symptomatic. For example, intestinal metastases can cause bowel obstruction and rectal blood loss. Symptomatic metastases can require local therapy to allow patients to start or to continue systemic treatment. Also, in case of a heterogeneous response to immune checkpoint inhibitors, with the majority of lesions responding, single non-responding metastases are increasingly treated with local therapy aiming to achieve durable responses. Furthermore, there is a need for reliable biomarkers that can predict an early response to systemic treatment and ensure a timely switch of treatment in case of ineffectiveness. In addition, the diagnostic work-up and follow-up of melanoma have changed. Early detection of metastatic disease in patients with high-risk melanoma has become more important with the availability of more effective systemic treatment options. The current clinical guidelines are, however, not clear about which imaging technique and in which stage of the disease imaging studies should be used in the follow-up of melanoma. Mutation analysis has become more important as part of the diagnostic process with the introduction of BRAF-targeted therapy. Mutation analysis could be further improved and readjusted to the demands of certain clinical situations.

Rectal cancer

Colorectal cancer is the third most common cancer globally, and in roughly a third of the cases the tumor is located in the rectum. The risk of rectal cancer increases with age, with a median age of 70 years. Other important risk factors mainly involve lifestyle, i.e. diets low in fiber and high in meat, smoking and excessive alcohol use.[22] The majority of rectal cancers are adenocarcinomas. These adenocarcinomas are often diagnosed at a locally advanced stage and distant metastatic spread to the liver and lungs are also frequently encountered.[23]

For proper staging of rectal carcinoma, a complete colonoscopy is required. For local staging of large rectal tumors an MRI is the best imaging modality, whereas for local staging of T1-T2 tumors a rectal ultrasound is performed.[24] A CT scan of chest and abdomen is most appropriate for distant staging.

Surgery is the cornerstone of treatment. The type of surgery is dependent on the local extent of the tumor and location in the rectum. Superficially growing small rectal tumors (T1) can be managed using transanal local excision techniques. More invasive tumors require a transabdominal resection of the tumor, for which total mesorectal excision (TME) surgery is the standard, which is accomplished by a sharp dissection around the mesorectal envelope.[25] Roughly all tumors within 5 cm of the anal sphincter are managed with an abdominoperineal resection and more distal tumors are managed with a low anterior resection. Locally advanced rectal tumors require downstaging with preoperative radiotherapy or chemoradiotherapy to achieve adequate resection margins. Long-course radiotherapy in combination with 5-fluorouracil-based chemotherapy is the standard for locally advanced rectal carcinoma, its use has lowered the local recurrence rate to less than 10%.[26] Furthermore, in 16% of the patients receiving neoadjuvant treatment a complete pathological response is seen in their surgical specimen.[27] This raised the question whether surgical resection could be prevented in these patients and if so which imaging studies should be performed to reliably detect a complete response and exclude metastatic disease. There is currently a trend towards applying a wait and see policy in patients with a clinical complete response to preoperative chemoradiotherapy.[28]

The management of patients with distant metastases is more individualized. Roughly 20% of the rectal cancer patients presents with synchronous distant metastases, mainly in liver and lungs.[29] In patients with limited metastatic spread, resection of both primary tumor and distant metastases should be pursued, but the timing and sequence of resection of the tumor locations is still matter of debate. Patients with irresectable distant metastases can be treated with palliative systemic therapy. Combination chemotherapy with fluoropyrimidine in combination with irinotecan or oxaliplatin is standard of care in the first line and can be combined with anti-VEGF or anti-EGFR targeted agents.[29-31]

Molecular analysis of tumors is becoming more important because of the availability of targeted drugs. The European guidelines advise to perform RAS and BRAF mutational analysis at the time of diagnosis of metastatic disease.[32] RAS mutation analysis is mandatory because tumors with activating mutations in RAS are resistant to anti-EGFR therapy.[33] BRAF mutations in colorectal cancer are also associated with anti-EGFR therapy resistance and with a poor prognosis in general.[34] Microsatellite instability analysis is also important as these tumors are sensitive to treatment with immune checkpoint inhibition.[35, 36]

Aim of this thesis

The development of new classes of systemic treatments, i.e. targeted therapy and immune checkpoint inhibitors, and the improvements in and new indications for surgical management of cancer have improved the prospects of cancer patients in the past decades. These new treatment strategies have introduced new indications, new (severe) adverse events and have resulted in an increase in costs. Therefore, optimal selection of patients for the right treatment is required. In this thesis we explored how imaging and biological markers can be used to identify patients that could benefit most from specific treatment strategies in melanoma and rectal cancer.

Outline of the thesis

The current international guidelines on melanoma advise staging of advanced melanoma with contrast-enhanced CT (ceCT) or ^{18}F-FDG PET/CT scans. An ^{18}F-FDG PET/CT scan is ^{18}F-FDG PET combined with a low-dose, non-contrast-enhanced CT. In contrast to ceCT, ^{18}F-FDG PET/CT provides both metabolic and anatomical information. In the review in **chapter 2** the role of ^{18}F-FDG PET/CT in stage IV melanoma was explored. The performance of ^{18}F-FDG PET/CT in the detection of distant metastases was compared to ceCT, whole-body MRI and targeted imaging approaches. Also, the ability of ^{18}F-FDG PET/CT to predict or monitor a response and/or toxicity to the novel systemic treatment options in metastatic melanoma was studied. Technical aspects, cost-effectiveness and suggestions for future research with regards to ^{18}F-FDG PET/CT in melanoma were also discussed.

An activating mutation in the BRAF gene is an important genomic biomarker for systemic treatment of metastatic melanoma. Patients with BRAF-V600 mutated melanoma are eligible for treatment with BRAF and/or MEK inhibitors. The DNA sequencing techniques that are currently used for BRAF mutational analysis are, however, time-consuming and

in certain clinical situations there is a demand for a rapid mutation test. In **chapter 3** three rapid BRAF tests: immunohistochemistry using the BRAF-VE1 antibody, BRAF-V600E mutation droplet digital PCR test and a fully automated, real-time PCR test (Idylla), were compared to the conventional BRAF mutation test using High Resolution Melting analysis/Sanger sequencing to find the most suitable rapid test for clinical use.

S100B is a well-known serum biomarker for melanoma. This calcium-binding protein is highly expressed in melanoma cells and can be detectable in serum. It is a prognostic marker in all stages of melanoma and is used as a marker of distant relapse in the follow-up of high-risk melanoma. Less is known about the ability of serum S100B to predict a response to systemic treatment in metastatic melanoma. Especially for systemic treatment with immune checkpoint inhibitors, in which responses are often late and can be preceded by temporary tumor growth, there is a high need for a reliable early biomarker. Therefore, we studied the ability of serum S100B to determine an early response to immune checkpoint inhibition in **chapter 4**. For this purpose, we compared changes in serum S100B level to change in tumor burden on CT early during treatment with both CTLA-4 and PD-1 checkpoint inhibitors.

Treatment with immune checkpoint inhibitors can lead to immune-related adverse events. Previous studies have shown a positive association between these adverse events and treatment efficacy of CTLA-4 and PD-1 immune checkpoint inhibitors, both in melanoma and other tumor types. **Chapter 5** focusses on adverse events in a cohort of 147 advanced melanoma patients that were treated with pembrolizumab (anti-PD-1) in an expanded access program in the Netherlands. An association between adverse events and efficacy in terms of disease control rate and progression-free and overall survival was assessed correcting for important covariables.

The introduction of new systemic treatment options for melanoma in the past decade have changed the prognosis of metastatic melanoma patients. In particular treatment with immune checkpoint inhibitors can result in long-term survival. Because of this change in prognosis for metastatic melanoma patients the approach to patients with intestinal metastases has also changed. In **chapter 6** the optimal imaging and treatment strategy for melanoma patients with intestinal metastases was explored in a cohort of 21 patients with intestinally metastasized melanoma. A treatment algorithm was constructed to aid in treatment decision making involving multiple disciplines.

Locally advanced rectal cancer is treated by chemoradiotherapy followed by total mesorectal excision surgery. Optimal staging of these patients is well established and consists of a pelvic MRI for local staging and CT of chest and abdomen for distant staging. Because of the long duration of chemoradiotherapy followed by an interval of at least 6

weeks between chemoradiotherapy and surgery, a restaging CT scan is performed of chest and abdomen to rule out the development of distant metastases that were not detectable at baseline. We determined the value of this restaging CT scan in **chapter 7** by studying the impact of the restaging CT scan on treatment strategy. This study was performed in a retrospective cohort of 153 locally advanced rectal cancer patients treated at two Dutch centers.

The optimal treatment for rectal cancer patients with synchronous distant metastases is not well established. Between 2006 and 2010 a phase II trial was conducted in primary metastatic rectal cancer patients who were treated with a chemoradiotherapy regime that consisted of short-course radiotherapy followed by a combination of capecitabine, oxaliplatin and bevacizumab and eventually followed by surgical treatment of all tumor sites. We performed a long-term follow-up of this cohort in **chapter 8** and determined the long-term results of this study regimen in terms of overall and recurrence-free survival. The impact of the radicality of surgery and pathological response to neoadjuvant treatment as biomarkers of survival were also studied.

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