Interventional oncology in the management of breast and kidney cancer

Citation for published version (APA):

Document status and date:
Published: 01/01/2020

DOI:
10.26481/dis.20201023ba

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.
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Valorisation
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Since cancer is the second leading cause of death worldwide, research towards improvement of diagnosis and treatment stratification is needed. During the recent years, the treatment of cancer has improved the survival rates of cancer patients tremendously. However, it has been stated that cured cancer patients have a poorer quality of life as a consequence of the late effects of the treatments. Subsequently, minimally invasive treatments with lower morbidity rates have been increasingly adopted as treatment option for cancer care.

Interventional oncology (IO) uses image-guided procedures with the aim to prolong survival and maintain quality of life. During the last decade, IO procedures have frequently been used in clinical practice and are adapted in several international guidelines. IO procedures are able to provide the diagnosis of cancer by performing biopsies, treat patients in a curative or palliative setting and provide symptom control. Almost every cancer patient undergoes one sort of IO procedure and improvement of these procedures are therefore essential for cancer patients.

To provide minimal invasive IO treatment, data is necessary to select the best patient population to achieve the highest efficacy rates. In this thesis, we investigated the efficacy and safety of intra-arterial liver directed therapies in liver metastatic breast cancer (LMBC) patients and percutaneous ablation in patients with renal cell carcinoma (RCC). We analyzed relatively large cohorts, enabling us to determine factors influencing the outcome of the interventional oncology procedures.

Part I: Intra-arterial therapies for liver metastatic breast cancer
Breast cancer is the second most diagnosed cancer type and the fourth cause of death in the Netherlands. When breast cancer is diagnosed at an early stage of the disease, curation is often possible. Contrary, LMBC has a poor prognosis with survival rates up to 3 years. Standard treatment for LMBC is systemic treatment by means of chemotherapy or (hormone) targeted treatment. Many patients develop toxicities from the chemotherapy which impairs quality of life or become chemo refractory to the systemic treatment. Intra-arterial therapies are liver directed IO procedures performed under image guidance to provide local control in the liver at minimal side effects that can be administrated in chemo refractory LMBC patients or function as chemo holiday in LMBC patients.

In the Netherlands, intra-arterial therapies are registered for patients with primary liver tumours, colorectal liver metastases or neuroendocrine neoplasma. To date, intra-arterial therapies are not regularly performed as
treatment in the Netherlands in LMBC patients, mainly because LMBC patients often have extra-hepatic disease and will consequently only receive chemo or targeted therapy. However, liver metastases may cause impairment of liver function and therefore especially endangers the patient’s life. Intra-arterial therapy can than function as a minimal invasive technique to control the liver metastases and improve quality of life. With the results of this thesis, the awareness of this treatment option for LMBC patients has increased in Europe and the Netherlands.

Mitomycin C (MMC) infusion is an intra-arterial therapy whereby a chemotherapeutical (MMC) is administrated via intra-arterial access in the hepatic arteries every four weeks. It is a relatively easy and inexpensive procedure for interventional radiologists that can be performed in many centers in the Netherlands. Only a one-day hospital observation is required for this procedure and most patients experience these treatments as innocent with resume of daily life within a few days. Intra-arterial therapy by MMC infusion is not a new innovative procedure, but expands the toolbox of treatment options for LMBC patients with a minimal invasive treatment option.

This thesis added to the knowledge of MMC infusions by reporting on one of largest cohort of LMBC patients treated with MMC. We determined which patients benefit the most from the intra-arterial therapy and observed a worse overall survival in patients with an increased number of prior therapies, upfront deteriorate liver function and excessive tumor burden. Our data has been presented at (inter) national congresses to achieve recognition for this therapy. With these results, we can further implement MMC infusion in the Netherlands and determine in advance which patients may benefit the most from the treatment. Furthermore, interventional radiologists can council patients in advance of the MMC infusion with expectations based on a large cohort.

This thesis also includes an innovative treatment combination of two intra-arterial therapies which was not reported before in LMBC patients. We showed that sequential therapy by MMC and Yttrium-90 is feasible and safe. Patients with liver dominant disease can be treated for a longer period by intra-arterial therapy to control the liver disease. However, 30% of the patients could not receive the combination treatment due to extra-hepatic disease progression. This raises the question if the sequential treatment of two intra-arterial therapies is the best treatment option. Maybe a combination with systemic treatment would be more beneficial for LMBC patients. With these reports important factors have been determined to develop future studies for LMBC
patients and hopefully inspires more clinicians to use intra-arterial therapies in LMBC patients.

**Part II: Percutaneous ablation in renal cell cancer**

Patients with stage I RCC have excellent outcomes with 10-year survival rates between 95 and 100% after elimination of the tumour. In the past decade a more minimal invasive nephron sparing treatment approach has therefore been accepted as a treatment option. Patients that were previously treated with removal of the entire kidney (radical nephrectomy), can now undergo a partial nephrectomy (PN). Compared to PN, percutaneous ablation is associated with a lower comorbidity and mortality with excellent preservation of the kidney function.

During percutaneous ablation extreme high or low temperatures are conducted via needles for tumour destruction. Over the last years, percutaneous ablation has increasingly been used for treatment of small renal masses. Patients treated by percutaneous ablation have a reduced number of hospital day admissions and lower complications rates compared to PN. In this thesis, we defined some of the factors that may add to the knowledge of percutaneous ablation and provide the least invasive treatment for RCC patients.

We showed that by performing the biopsy before the planned ablation procedure, patients have the opportunity to deliberate on the treatment with the physician, thereby reducing overtreatment and providing essential information for treatment stratification. The outcome of this study affected the management of RCC patients in clinical practice of the renal cancer network Amsterdam. Patients with a T1a RCC whom are planned for ablation now first undergo a biopsy, as opposed to previous management in which patients received a biopsy during the ablative treatment. In the future also other centers in the Netherlands will adopt this management, which will reduce unnecessary treatments of patients with a renal mass in the Netherlands.

Microwave ablation (MWA) is a relatively newer ablation technique with less reports available. In chapter 6 we showed that MWA is a safe and effective treatment for T1 RCC and is most effective and safe in smaller peripheral tumours. We determined that size and location are key to obtain a complete treatment in MWA. Hence, our results will help to select the right patient for the best oncological outcome in T1 RCC and hopefully motivate physicians to use the MW system for renal ablations in this patient population.
Percutaneous ablation is not generally accepted and widely used as treatment in T1b tumours with limited reports available. This thesis describes two ablation techniques for large tumours, namely; MWA and cryoablation. We showed that MWA for T1b lesions was feasible, only 50% of the patients needed a subsequent treatment following MWA which should be considered beforehand. In addition, we reported the outcome of patients whom were treated with cryoablation after failure of MWA with a 100% success rate in four patients with a T1b tumours. Our results are promising for cryoablation in T1b tumours, yet larger reports are needed. This thesis therefore functions as inspiration for future research for minimal invasive treatment option in RCC patients.

Last, another innovative treatment modality has been described in this thesis, namely the combination of cryoablation and immunotherapy. Immunotherapy has showed a remarkable survival gain for several cancer types. Unfortunately, not all patients respond to the immunotherapy, due to, among others, escapement of cancer cells to the immune system. Percutaneous ablation may prime the immune system by providing a pool of cancer specific antigens that can initiate a specific immune response against the cancer cells. This thesis investigated the evidence of cryoablation and immunotherapy in different cancer types. Most included studies in the critical review described a positive effect of the combination therapy regarding survival and implies that future research in this field might be of great benefit.