Optimizing the treatment of oesophageal cancer

VALORIZATION ADDENDUM

The scientific results of this thesis will be described in perspective of the valorization process regarding its value for society, its economic relevance and novelty of this work.

Clinical and social relevance

Our thesis primarily focused on oesophageal cancer, which currently is the eight most common cancer type worldwide and the sixth most common cause of death from cancer. In 2017, more than 2500 patients were diagnosed with oesophageal cancer in the Netherlands. The rise in risk factors suchs as obesity and gastro-oesophageal reflux disease will lead to an increased incidence of this cancer.

Due to the aggressive character of the tumour and the lack of effective individualized treatment, the 5-year survival rates and quality of life of patients with oesophageal cancer is poor.

Still, large individual differences in survival and treatment response are observed which emphasize the need for more personalized therapy. Radiation therapy will play a central role in this personalized medicine era together with the development of new drug agents and repurposing others according to radiobiological rationale.
The main theme of this thesis is the development of a clinical guidance for radiation treatment in oesophageal cancer and investigate the role radiomics and hypoxia in the prognosis to define a more tailored therapeutic approach of this disease.

PART I may serve as a ”template” to guide oesophageal cancer treatment and target delineation in daily practice for the radiation oncologist. Previous studies have shown that microscopic extension outside the clinical target volume is an unfavourable prognostic factor for disease-and overall survival. With the results of chapter 1, we can reduce unnecessary irradiation of lymph node regions with minimal risk of tumour involvement and still assure adequate covering of microscopic target areas. With chapter 2 and 3, we further attempt to minimize inconsistency of the irradiation field and to achieve precise radiotherapy.

The “drug repurposing “ and “radiomics” approach in *PART II* may contribute to the ongoing movement towards more individualized treatment strategies for oesophageal cancer patients. The strategy of radiomics is not yet ready to be implemented on a larger scale in standard clinical practice. However, it can fit in within existing practice with low cost and without an additional burden to patients, as it involves post-processing techniques on standard CT which are performed as part of routine clinical practice.

Our data presented in chapter 5 with metformin support the data found in lung cancer and could also be of interest for other cancer patients. In addition, metformin is an inexpensive drug and might and could be a safe efficacious approach to overcome tumour hypoxia in radiation treatment.

The studies presented in *PART III* are an attempt at improving neoadjuvant treatment response. In this respect, there might be a subpopulation where complete response directs to a watch-and-wait strategy without debilitating surgery. In chapter 6, we describe the role of hypoxia in oesophageal cancer which can be used for selection of patients with hypoxic properties, known for its negative impact on the prognosis of the patients. Although our paper of hypoxia-associated markers in oesophageal cancer involves mostly preclinical data, we were the first to assemble crucial information of the role of hypoxia parameters in these patients.

From an economically perspective stratifying patients into being hypoxic or not could be cost-effective when using anti-hypoxia treatment. In chapter 7, we propose a phase I window-of-opportunity trial with the combination of TH-302, an hypoxia-activated prodrug and chemoradiotherapy. It is with this study that we hope to improve the response to treatment in selected oesophageal cancer patients. The study was prepared with Threshold Pharmaceuticals , a biotechnology company that develops tumour-targeted therapies. One of its products is [18F]-Hx4, an in-licensed positron-emission tomography agent for hypoxia. The use of this imaging biomarkers allows us assessment of any early anti-tumour activity of evofosfamide or TH-302.

Using new theragnostic and therapeutic opportunities (hypoxia-radiomics imaging, combination with a bioreductive drug) will result in a major benefit for patients with oesophageal cancer. With the emerge of individualized medicine and the increasing amount and complexity of available medical data, a growing need exists for the development of clinical multifactorial decision-support systems based on prediction models of treatment outcome.

MAASTRO Clinic has extensive expertise in developing prediction models for survival with published series in major American and European radiotherapy journals (www.predictcancer.org). MAASTRO Clinic established a data warehouse to collect, relate and interpret clinical, imaging, treatment and molecular data from patients (see also www.cancerdata.org) which been recorded in an electronic patient database since 2005. This warehouse includes patients records, registry data, molecular profiles, clinicopathologic data, treatment data and raw DICOM images. In future, we hope to develop a truly useful predictive model in oesophageal cancer which can be integrated in the clinic shaded on in a global manner. Eurocat (www.eurocat.info) is a project managed by Maastro Clinic with the ambition to do so.

Target audience

PART I of this thesis is an effort moving towards a uniform radiation approach in patients with oesophageal cancer. More particularly, radiation oncologists can individualize regional lymph node irradiation according to tumour location and thereby avoid unnecessary lung and heart radiation dose. Consequently, surgeons are confronted with less postoperative complications like radiation pneumonitis and anastomotic leakage.

In the current healtch care environment there is also a growing interest for patient-aided treatment decision. We present the use of radiomics and presence of hypoxia which can be of use in the implementation in treatment decision tools (www.oncoradiomics.com) . Finally, the effect of hypoxia presence in oesophageal cancer and anti-hypoxia treatment could be of interest to all healthcare companies with interest to develop hypoxia targeted agents. For example, the development of Evofosfamide has shifted focus from the combination with chemotherapy to immunotherapy. (https://clinicaltrials.gov/ct2/show/NCT03098160?cond=evofosfamide&draw=2&rank=1).

Novelty of the concept

Adequate radiotherapy delineation and delivery is of upper most importancy when overthinking deferral of consequent surgery. Even with 'old' data this PhD thesis is the first to overview the role of elective lymph node irradiation in oesophageal cancer and to implement delineation guidelines according to tumour location.

Extraction of multiple features from CT images as in radiomics is a recent innovative way of using data for defining the tumour phenotype. This innovative form of quantitative image analysis has future potential for clinical practice in patients with oesophageal cancer by providing an additional layer of information to the standard imaging assessment.

Evidence of the negative prognostic role of hypoxia presence is not new but is accumulating and still rather limited in oesophageal cancer. This thesis provides an overview of the current data of hypoxia presence in oesophageal cancer and paves the road for anti-hypoxia treatment in patients with oesophageal cancer. Threshold is a clinical stage biopharmaceutical company focused on the discovery and development of cancer therapeutics based on a novel and powerful approach of targeting this tumour hypoxia. In our phase I trial with TH-302 we are the first to describe a window-of-opportunity trial with a hypoxia-activated prodrug in this disease. In particular, the combination of TH-302 and radiotherapy is a novel concept.

The aim is to exploit these prodrugs to sensitize tumours to the conventional chemo-radiotherapy and improve the therapeutic outcome in oesophageal cancer patients.

Road to the market

There is no doubt that oesophageal cancer deserves more research and there is a need to seek for biomarkers of response and prognosis to adapt treatment. The studies presented in part I to III are examples of initiatives to improve personalized oesophageal cancer treatment.

First effort to uniform radiotherapy treatment volume and preparation have been made with our research. The conclusions presented within this first part of the thesis can be recommended guidelines for routine clinical practice on a worldwide basis.

In addition, revealing radiomics and hypoxia data in oesophageal cancer is just the start of a new paradigm in treating this malignant disease. Medical imaging has been

the cornerstone for the management of patients for decades, particularly in oncology. Improved standardization of image feature extraction in combination with artificial intelligence will guide personalized treatment in the nearby future.
Both, hypoxia-associated biomarkers and radiomic features have potential to be implemented for clinical decision support systems to select the best tailored treatment. In PART III of this thesis, we present new initiatives to implement hypoxia PET imaging which lead to new opportunities regarding clinical trials. In March 2013, Threshold announced the acquisition of [^{18}F]Hx4 from Siemens Healthcare. [^{18}F]Hx4 is an investigational radiolabeled Positron Emission Tomography (PET) tracer for hypoxia. [^{18}F]Hx4 could be potentially be used as a companion diagnostic to hypoxia-targeted therapeutics based on Threshold's drug discovery platform. The initial intent is to develop [^{18}F]Hx4 to determine a patient's tumour hypoxia profile, which may identify patients who will best respond to Threshold's hypoxia-targeted therapeutics.

Consequently, implementation of new hypoxia radiosensitizers to improve treatment might find their way to the market (www.convertpharma.com) . This next step could be realised by finishing the trial in oesophageal cancer with hypoxia-activated prodrugs in a window-of-opportunity trial.

We acknowledge that a variety on disease-related information e.g. patient and family history, pathology and many other data will be needed to be part of a well-founded treatment decision. We are not there yet, but we are hopeful that analysing vast amount of medical Big Data data from a worldwide population of oesophageal cancer patients will allow us to improve the effectiveness of certain treatments and exclude those which don't.

This tailored treatment will definitely benefit society as the approach will become more effective and more cost-efficient.